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SEASONAL AWARENESS AND ALERT LETTER (SAAL)

For Epidemic-prone infectious diseases in Pakistan

Summer-Monsoon Season

OBJECTIVES OF SAAL

- To alert concerned health authorities and professionals at all levels about the epidemic-prone infectious diseases in the Summer-Monsoon season
- To facilitate the preparations for timely and efficient response to the encountered alerts / outbreaks and thus reduce the associated morbidity and mortality

DATA SOURCES

The available national data collected during 2012 to 2017 by FE&DSD from Disease Early Warning System (DEWS), Provincial Health Departments, Provincial Disease Surveillance & Response Units (PDSRUs), Expanded Program on Immunization (EPI), Acute Viral Hepatitis Sentinel Surveillance Program, Directorate of Malaria Control and laboratory based data from NIH has been analyzed to see the exhibited patterns of high priority communicable diseases.

The description of all priority diseases has been arranged in alphabetical order. Additionally, under the section of National Potential Public Health Events, technical details on Naegleria fowleri infection, extensively drug resistant typhoid strain and heat stroke have been included. Ebola Virus disease, Nipah virus, Middle East Respiratory Syndrome Corona virus (MERS CoV) infection, and Yellow Fever have been shared as International Potential Public Health Events.

Outbreak - Prone Diseases	Alerts
Chikungunya	
Crimean Congo Hemorrhagic Fever (CCHF)	
Dengue Fever	
Diphtheria	
Gastroenteritis (Acute)	
Leishmaniasis	
Malaria	
Measles	
Meningococcal Meningitis	
Pertussis	
Poliomyelitis	
Typhoid Fever	
Viral Hepatitis (Acute)	

	High Alert- peak occourrence in the Summer-Monsoon season
	Medium Alert - cases will be encountered and any show up as an outbreak

CHIKUNGUNYA

Introduction: Chikungunya is a mosquito-borne viral disease which was first reported in southern Tanzania in 1952. In Pakistan, cases were reported from different areas especially from Karachi, Haripur, Islamabad and Rawalpindi[1].

Clinical Picture: Fever, arthralgia, myalgia, headache, nausea, fatigue and rash. Serious complications are not common with occasional cases of ocular, neurological and cardiovascular complications. There are rare reports of spontaneous abortions and mother-to-child transmission in perinatal period[1].

Infectious Agent: Chikungunya belongs to an alpha virus genus *Togaviridae* family, and is a heat-sensitive RNA virus[1].

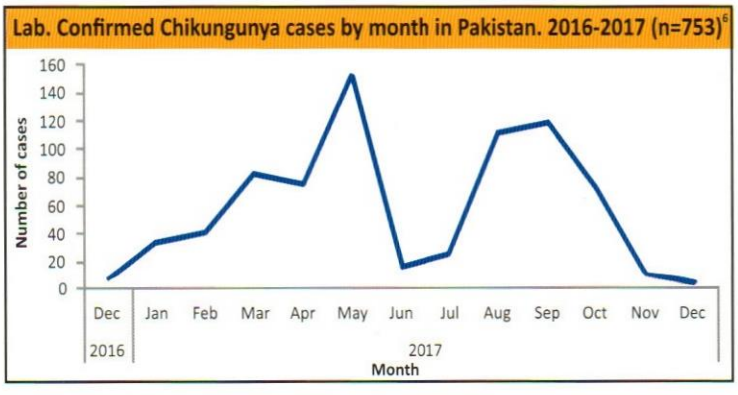
Reservoir: Non-human and human primates are likely the main reservoirs[2].

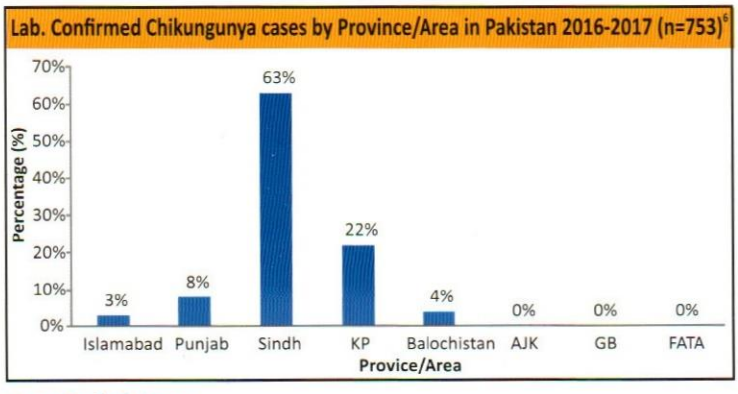
Mode of transmission: Transmit through bite of infected female Aedes aegypti and Aedes albopictus mosquitoes[1].

Incubation period: Onset of illness occurs usually between 4-8 days but can range from 2 to 12 days[3].

Communicability: CHIKV infections cause high level of viraemia, which typically lasts 4-6 days, but can persist for up to 12 days after the onset of illness[4].

Seasonality: Chikungunya can spread all year round. Warm humid weather and stagnant water breeds the mosquitoes that carry the virus, which is why an epidemic is most likely to occur during post-monsoon periods[5].





Case Definitions:

Suspected Case: Any person with an acute onset of fever >102°F (38.5°C) and severe arthralgia/ arthritis not explained by other medical conditions[7].

Probable Case: Any suspected case residing or visited endemic areas within 15 days prior to the development of symptoms[7].

Confirmed case: Suspected/ probable case confirmed by any of the following laboratory tests:

- RT-PCR within one week after onset of illness
- Serological detection by IgM ELISA after 4 days of the onset of illness
- Four-fold rising of IgG titers in samples collected at least three weeks apart[7]

Specimen Collection and Transportation: Collect 3-5 ml venous blood/ serum of suspected patient in sterile venoject tubes. Tight and seal it with full biosafety precautions. Label and pack it properly in triple packing with ice packs and transport to laboratory along with complete history form[8]. Transport the sample to the Virology Department of PHLD at National Institute of Health, Islamabad if the diagnostic facility not available in the particular area.

Case Management:

There is no specific antiviral drug for Chikungunya. It is a self-limiting disease and treatment is directed primarily at relieving the symptoms, including the joint pain by using anti-pyretic, optimal analgesics and rest[9].

Preventive measures & vaccination:

- No vaccination available
- Minimizing vector population: Intensifying efforts to reduce larval habitats in and around the houses
- Minimizing vector-patient contact
- Using bed-nets (preferably Permethrin-Impregnated nets)
- Wearing full-sleev clothes to cover extremities
- Using Wire-mesh/ nets on doors and windows[10].

References:

References are available in online version at www.nih.org.pk

CRIMEAN-CONGO HEMORRHAGIC FEVER (CCHF)

Introduction: A tick-borne zoonotic viral disease that is asymptomatic in infected animals, but a serious threat to humans[1]. Human infections begin with nonspecific febrile symptoms, but progress to a serious hemorrhagic syndrome with a high case fatality rate (10-40%)[2]. It is one of the most widely distributed viral hemorrhagic fevers occurring in parts of Africa, Middle East, Asia and Europe[3]. The occurrence of this virus is correlated with the distribution of Hyalomma tick species (Principle vector)[4]. CCHF is endemic in Pakistan with sporadic outbreaks.

Clinical Picture: Sudden onset with initial signs and symptoms including headache, high fever, back pain, joint pain, stomach pain, vomiting, red eyes, flushed face, red throat, and petechiae (red spots) on the palate are common. Symptoms may also include jaundice and in severe cases, changes in mood and sensory perception. With illness progression, large areas of severe bruising, severe nose bleeds and uncontrolled bleeding at injection sites can be seen, usually beginning on the fourth day of illness and lasting for about two weeks[5].

Infectious Agent: Crimean-Congo Haemorrhagic Fever (CCHF) Virus belongs to *Bunyaviridae* family[1].

Reservoir: Hyalomma tick, domestic animals, such as cattle, goats, sheep, rodents such as hedgehog, rats, hares and birds are generally resistant with the exception of Ostrich[6].

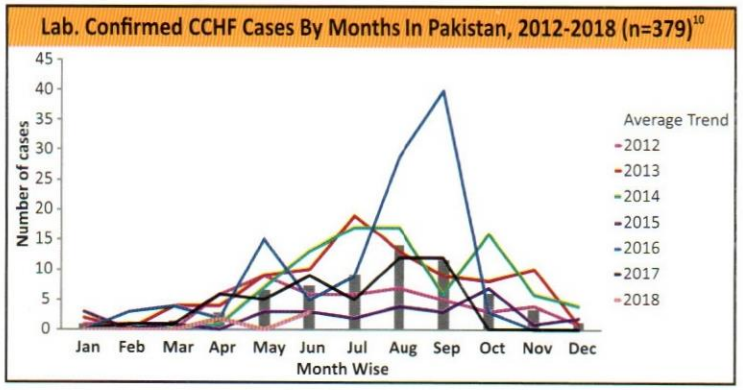
Mode of transmission:

Bite of infected Hyalomma tick (vector), handling of tick infested animals, direct contact with blood/ tissue of infected domestic animals (slaughtering); or direct contact with blood/ tissue of infected patients. Nosocomial infections are common[7].

Incubation Period:

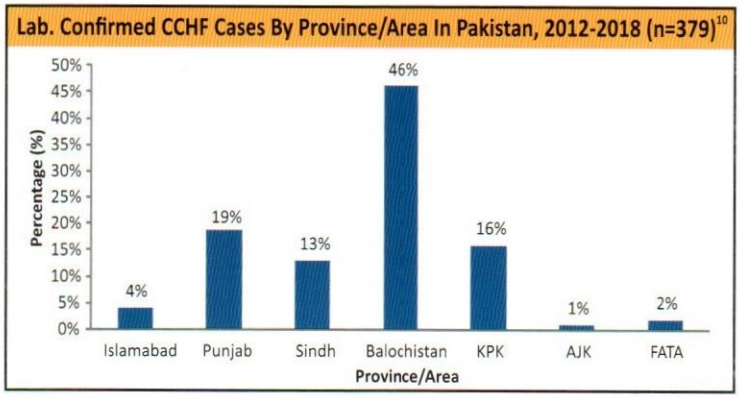
- 1-3 days after tick bite
- 5-6 days after exposure to infected blood or tissues with a maximum of 13 Days[8].

Seasonality: Surge of cases occur during fall and spring seasons, associated with life-cycle of ticks, exposure of new born animals, exposure of migrating animals[9].



Geographical Distribution in Pakistan:

Since the diagnosis of first human case of CCHF in 1976, the sporadic cases have continued to occur all over Pakistan and predominantly in Balochistan[10].



Alert Threshold: One probable case is an alert and requires an immediate investigation[11].

Outbreak Threshold: One lab confirmed case of CCHF is an outbreak[11].

Case Definitions:

Suspected Case: Any person with sudden onset of fever over 38.5°C for more than 72 hours and less than 10 days, especially in CCHF endemic areas and those in contact with livestock such as shepherds, butchers, animal handlers and health care personnel[11]

Probable Case: Suspected case with history of febrile illness of 10 days or less with epidemiological link AND any two of the following: thrombocytopenia less than 50,000/mm^3, petechial or purpuric rash, epistaxis, haematemesis, haemoptysis, blood in urine and/or stools, ecchymosis and gum bleeding[11].

Confirmed Case: Suspected/ probable case confirmed through PCR and/ or ELISA[11].

Laboratory Confirmation:

- Detection of viral nucleic acid by PCR in blood specimen
- Confirmation of presence of IgM antibodies in serum by ELISA (enzyme-linked immunoassay)[11].

Specimen collection, storage and transportation: Collect 3-5 ml of blood in vacutainer observing strict biosafety precautions. Keep in upright position to prevent haemolysis. Sample storage at 2-8°C.Transport to the laboratory in triple package with ice packs or frozen with dry ice along with complete lab request form.

Case Management

- Patients with probable or confirmed CCHF should be isolated and cared for using strict barrier-nursing techniques with recommended Infection Prevention & Control (IPC) Precautions i.e. standard plus contact precautions. Use additional precautions

(droplet/ aerosol) in case of any extensive contact/ procedure.

- Only designated medical, paramedical staff and attendants should attend the patient.
- All medical, paramedical staff and attendants should wear recommended Personal Protective Equipments (PPEs) before entering the isolation room and dispose the PPEs properly after use.
- All secretions of the patient and hospital clothing in use of the patient and attendants should be treated as infectious and where possible, clothings should be autoclaved before incinerating.
- Every effort should be made to avoid spills, pricks, injury and accidents during the management of patients. Needles should not be re-capped and discarded in proper safety disposal box.
- All used material e.g. syringes, gloves, cannula, tubing etc. should be collected in autoclavable bag and autoclave before incineration.
- All re-useable instruments should be decontaminated (5% bleach solution) and autoclaved before reuse.
- All surfaces should be decontaminated with 5% bleach solution.
- After the patient is discharged, room surfaces should be wiped down with 5% bleach solution to kill the virus and the room should be fumigated if risk of tick infestation[12,13].

Treatment: General supportive therapy is the mainstay of patient management in CCHF. Intensive monitoring to guide volume and blood component replacement is recommended. If the patient meets the case definition for probable CCHF, oral Ribavirin needs to be initiated immediately in consultation with the concerned physician. Studies suggest that Ribavirin is most effective if given in the first 6 days of illness. Oral Ribavirin: 30 mg/kg as loading dose, followed by 16 mg/kg every 6 hours for 4 days and then 8 mg/kg every 8 hours for 3 days[13].

Prophylaxis Protocol:

- The efficacy for post exposure Ribavirin in the management of hospital-associated CCHF, remain anecdotal.
- It may be given in a high loading dose (35 mg/kg orally followed by 15 mg/kg three times daily for 10 days) and only for high-risk settings (e.g. needle stick injury, mucous membrane contamination, emergency resuscitative contact or prolonged intimate exposure during transport) after baseline blood tests.
- Household or other contacts of the case who may have been exposed to infected ticks or animals, or who recall indirect contact with case body fluids should be monitored for 14 days from the date of last contact with the patient or other source of infection by taking the temperature twice daily. If the patient develops temperature of 38.5°C or greater, headache and muscle pains, he/she would be considered a probable case and should be admitted to hospital and started on Ribavirin treatment as mentioned bove[12].

Preventive measures & vaccination

- Educate public about the mode of transmission and about the means for personal protection.
- Persons living in endemic areas must be educated on:
  - Avoidance of areas where tick vectors are abundant, especially when they are active (spring to fall)
  - Regular examination of clothing and skin for ticks and their removal (without crushing them)
  - Wearing light-colored clothing covering legs and arms and using repellents on the skin.
  - Other measures, such as wearing gloves or other protective clothing to prevent skin contact with infected tissue or blood, may be taken by persons who work with livestock or other animals.
- For tick control animal dipping/ spraying in an insecticide solution. Injectable insecticide i.e. Ivermectin is also recommended.
- Butchers should wear gloves and other protective clothing to prevent skin contact with freshly slaughtered meat, blood and other tissues. Meat should drain 30 minutes, before distribution to public.
- Hospitals in endemic areas should ensure universal precautions in OPD and emergency rooms. Ensure injection safety measures and maintain stock of Ribavirin and PPEs.
- Bio-safety is the key element to avoid nosocomial infection. Patients with suspected or confirmed CCHF must be isolated and cared by using barrier-nursing techniques to prevent transmission of infection to health workers and others.
- In case of death of CCHF positive patient, family should be advised to follow safe burial practices.
- House wives, family and contacts - those with high risk exposures (needle stick, sharps, blood or body fluids contacts) should be observed for fever for 14 days. If fever develops, Ribavirin should be started immediately[12].

Guidelines Link: http://nih.org.pk/wp-content/uploads/2018/01/Guidelines-for-Crimean-Congo Haemorrhagic-Fever-CCHFUpdated-September-2013.pdf

References:

References are available in online version at www.nih.org.pk

ACUTE WATERY DIARRHEA (CHOLERA)

Introduction: Cholera is an acute, diarrheal illness caused by infection of the intestine with the bacterium *Vibrio cholerae*. An estimated 3-5 million cases and over 100,000 deaths occur each year around the world. Approximately one in 10 (5-10%) infected persons will have severe disease characterized by profuse watery diarrhea, vomiting and abdomen cramps. In these people, rapid loss of body fluids leads to dehydration and shock. Without treatment, death can occur within hours[1].

Clinical Picture: Cholera infection is often mild or without symptoms, but can sometimes be severe.

Reservoir of Infection: Humans are considered the primary reservoir and can be asymptomatic carriers[2].

Infectious Agent: *V. cholerae*

Mode of transmission: Infection results from ingestion of organisms in food and water or directly from person to person by faecal-oral route[3]

Seasonality: Throughout the year; higher incidence from April to November, in hot, humid and rainy season[6].

Geographical Distribution in Pakistan: During 2012 to 2017 in Pakistan, 76% (35,852) cases were reported from Punjab followed by Balochistan 15% (6,996) and Sindh 5% (2,353).

Incubation period: Few hours to 5 days[4]

Infectivity period: The contagious period for Cholera begins as soon as organisms are excreted in the feces. This can occur as early as about 6 to 12 hours after exposure to the bacteria and can last for about 7 to 14 days[5].

Alert Threshold: One case of AWD is an alert and must be investigated[7].

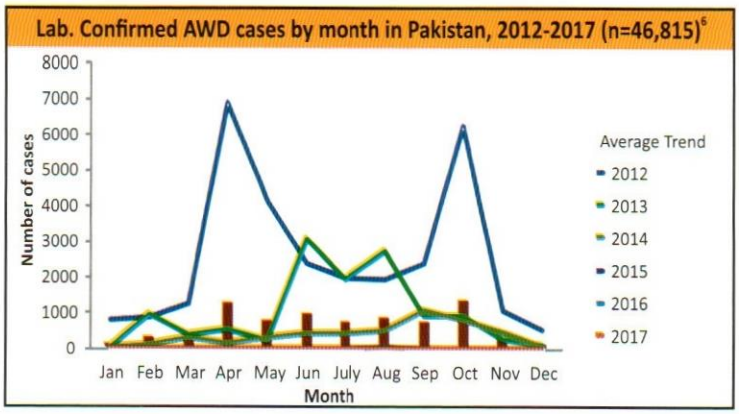
Outbreak Threshold: One lab confirmed case, or cluster of 6 or more suspected cases of AWD in one location is an outbreak[7].

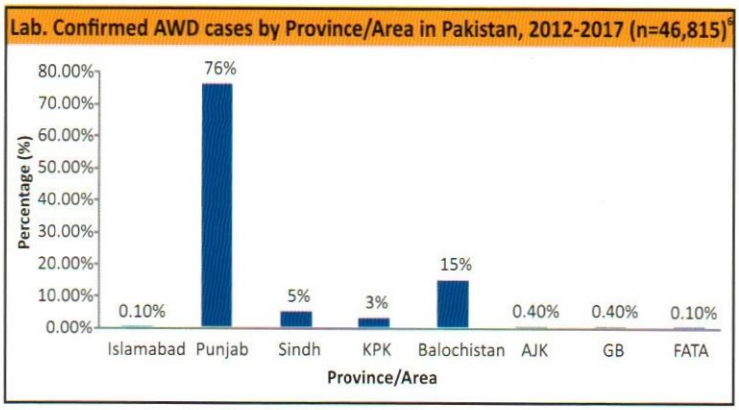
Case Definitions:

Suspected Case: Three or more abnormally loose or fluid stools in the past 24 hours with or without dehydration

Probable Case:

- Person aged over 5 years with severe dehydration or death from acute watery diarrhea with or without vomiting.





- Person aged over 2 years with acute watery diarrhea in an area where there is a Cholera outbreak[9].

Confirmed Case: Any suspected case confirmed through isolation of *V. cholerae 01 or 0139* from the stool[7].

Specimen Collection and Transportation:

- Place stool specimen in clean container and transport to laboratory in two hours of collection at room temperature
- If 72 hours delay, place stools soaked swab in Cary-Blair Medium.

Transportation: After proper labeling (date of collection, place of collection, name of the patient and other reference number as required), the specimens should be sent to the reference laboratory as early as possible. Cholera specimens in transport medium sent unrefrigerated will be useable in the laboratory for 7-14 days, depending on ambient conditions[8].

Case Management: Oral rehydration salt (ORS) should be given orally after every hour. Severely dehydrated patients require administration of intravenous fluids. Ringer's Lactate Solution (Hartman's Solution) is the preferred fluid for intravenous rehydration. Antibiotics (Doxycycline and Ciprofloxacin, Cefixime, Azaithromycin, Clathromycin, Erythromycin) reduce the duration of disease and period of excretion of V. cholerae in the stool of infected patients[7].

Preventive measures & vaccination: Ensuring adequate safe drinking water supply and proper sanitation. To make water safe for drinking, either boil the water or chlorinate it. All people (visitors or residents) in areas where cholera is occurring or has occurred should observe the following recommendations:

- Drink only bottled, boiled, or chemically treated water and bottled or canned carbonated beverages. When using bottled drinks, make sure that the seal has not been broken.
- To disinfect your own water, boil for 1 minute or filter the water and add 2 drops of household bleach or ½ an iodine tablet per liter of water.
- Avoid tap water, fountain drinks and ice cubes.
- Wash your hands often with soap and clean water.
- If no water and soap are available, use an alcohol-based hand cleaner (with at least 60% ethyl alcohol).
- Clean your hands especially before you eat or prepare food and after using the bathroom.
- Use bottled, boiled or chemically treated water to wash dishes, brush your teeth, wash and prepare food or make ice.
- Eat foods that are packaged or that are freshly cooked and served hot.
- Do not eat raw and undercooked meats and unpeeled fruits and vegetables.
- Dispose off feces in a sanitary manner to prevent contamination of water and food ources[4].

Vaccination: A single-dose live oral cholera vaccine called Vaxchora (lyophilized CVD 103-HgR) for adults 18 – 64 years old who are traveling to an area of active cholera transmission. Two other oral inactivated, or non-live cholera vaccines, Dukoral® and ShanChol®, are World Health Organization (WHO) prequalified[4].

References:

References are available in online version at www.nih.org.pk

MEASLES (RUBEOLA)

Introduction: Measles is a highly contagious viral disease mostly affecting children caused by measles virus of genus Morbillivirus which belongs to Paramyxoviridae family. Despite community vaccination coverage, Measles outbreaks can occur among under-vaccinated children and remains an important cause of death among young children globally. The virus spreads via droplets from nose, mouth or throat of the infected person[1]. Women infected while pregnant are also at risk of severe complications and the pregnancy may end in miscarriage or preterm delivery. Immunity after measles infection is life long, although there are few reports of measles re infection. The case-fatality rate may be as high as 25%[2].

Clinical Picture: Cough, coryza, conjunctivitis, fever, rash, photophobia, muscle pain, sore throat, tiny white spots inside the mouth (Koplik's spots) etc.[3] The occurrence of fever beyond the 3rd - 4th day of rash suggests a measles-associated complication. Measles can cause variety of clinical syndrome such as post measles infection(s) like pneumonia, lifelong brain damage/ neurologic syndromes i.e. acute disseminated encephalomyelitis (ADEM) and Sub-acute Sclerosing Pan Encephalitis (SSPE), deafness and death[4]. Severe measles is more likely among poorly nourished young children, especially those with insufficient vitamin A or whose immune systems have been weakened by other diseases[5].

Incubation period: Averages 14 days with a maximum range of 7-21 days[6].

Infectivity period: It can be transmitted by an infected person from 4 days prior to the onset of rash to 4 days after the rash erupts[7].

Alert threshold: One suspected case is an alert[7].

Outbreak threshold: Five or more clinical cases in a single location over a 30 days time with at least one lab confirmed case is an outbreak and requires investigation and response[7].

Case Definitions:

Suspected Case: A patient presenting with fever, generalized maculopapular rash with one of these: cough, coryza and conjunctivitis (3Cs)[8].

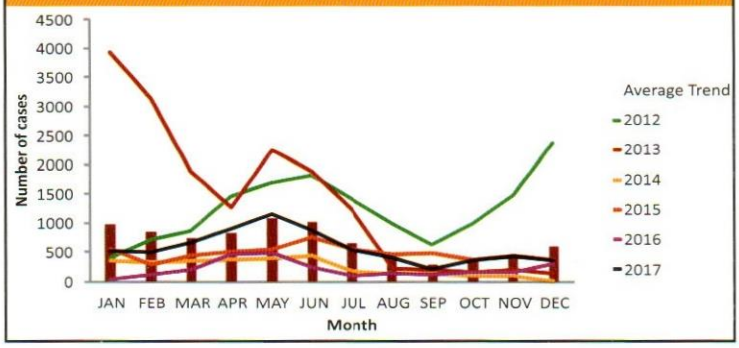
Confirmed Case: A suspected case, which is laboratory-confirmed or linked epidemiologically to a laboratory- confirmed case (positive IgM antibodies)[8].

Seasonality: Peak incidence in Pakistan is usually during April to May.

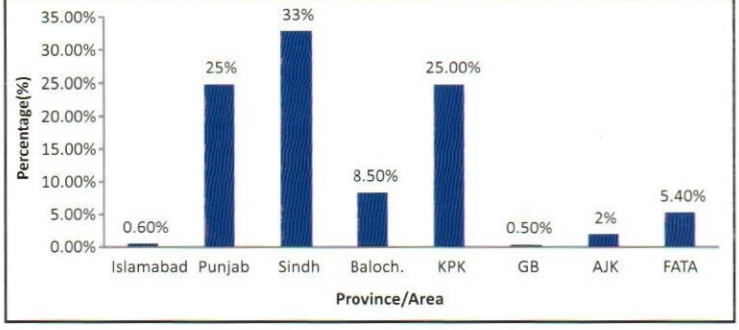
Geographical Distribution in Pakistan: During 2012-2017, Sindh remained the most effected province and has reported 33% (16,365) followed by Punjab and KP 25% (12,169) cases

Specimen Collection & Transportation: Collect throat swab for virus isolation, very early in the rash phase and preserve in Viral Transport Medium (VTM). Five samples should be taken from fresh cases, less than five days from rash onset, in documented outbreaks. Collect 5ml blood for serology. Store serum at 4-8°C and not for more than 48 hours. Do not freeze the whole blood. Transport the specimens in

Lab. Confirmed Measles cases by month in Pakistan, 2012-2017 (n=50,398)[9]



Lab. Confirmed Measles cases by Province/Area in Pakistan, 2012-2017 (n=50,398)[9]



triple packaged with complete request form by maintaining cold chain at 4-8°C[8].

Laboratory diagnosis: WHO recommends ELISA method as the gold standard for measles diagnosis. Anti-measles IgM is detectable in 3 - 30 days after the appearance of rashes. Anti-measles IgG is undetectable up to 7 days after rash onset and subsequently peaks about 14 days after the appearance of skin rashes[8].

Management:

Uncomplicated cases: The treatment is mainly supportive includes antipyretics and fluids. The WHO and UNICEF recommend Vitamin- A supplementation for 2 days with the dose of 50,000IU in <6 months, 100,000 IU in 6-11 months, 200,000IU in >12 months and for children with ophthalmologic evidence of Vitamin- A deficiency, doses should be repeated on day 2 and 28. Antibiotics should be prescribed to treat eye and ear infections and pneumonia. Complicated cases should be referred to the health facility after Vitamin- A supplementation[10].

Prevention and Control Measures: Immunize at risk population as soon as possible. Priority is to immunize children of 6 months to 5 years old, regardless of vaccination status or history of disease. Children who are vaccinated against measles before 9 months of age must receive a 2nd measles vaccination at 15 months. All children aged 6 months-5 years should also be administered prophylactic Vitamin- A supplementation[6].

References:

References are available in online version at www.nih.org.pk

Poliomyelitis

Introduction: Potentially fatal viral infectious disease that can affect nerves and can lead to partial or full paralysis[1]. Poliomyelitis is caused by Poliovirus which belongs from subgroup *Enterovirus* and *Picornaviridae* family. Poliovirus have three serotypes *P1, P2* and *P3* and each is capable of causing paralysis[2]. Humans are the only known reservoir and the disease is transmitted person-to-person mostly through the Oro-fecal route[1]. Cases are most infectious from 7-10 days before and after paralysis onset[3]. There are three basic patterns of Polio infection: sub clinical infections, non-paralytic, and paralytic. Clinical Poliomyelitis affects the CNS and is divided into non-paralytic and paralytic forms[4].

There is no cure, but there are safe and effective vaccines. The strategy to eradicate Polio is therefore based on preventing infection by immunizing every child until transmission stops and the world is Polio-free. Global public health efforts are ongoing to eradicate Polio by immunizing every child and focusing on pockets of missed children[5]. Polio was declared a Public Health Event of International Concern (PHEIC) by WHO on 5th May 2014[6].

Government of Pakistan has also declared Polio as an Emergency Program. The year 2017 showed the lowest ever annual number of Polio cases in the country but Poliovirus continues to be isolated through environmental surveillance over a significant geographical range[7].

Lab. Confirmed Polio cases by Province/Area in Pakistan, 2012-2018

Province/Area	2012	2013	2014	2015	2016	2017	2018
Islamabad	0	0	0	0	0	0	0
Punjab	2	7	5	2	0	1	0
Sindh	4	10	30	12	4	2	0
KP	27	11	68	17	7	1	0
Balochistan	4	0	25	7	1	3	3
GB	1	0	0	0	0	1	0
AJK	0	0	0	0	0	0	0
FATA	20	65	179	16	2	0	0
Total	58	93	307	54	14	8	3

Incubation Period: 7 - 14 days for paralytic cases (range 3 - 35 days)[8].

Seasonality: The ability of the Polio virus to infect children increases in high temperature due to which most of the cases are reported from May to September (High Transmission Season - HTS). In low temperature, from October to April, the virus remains less active[9].

Alert Threshold: One case is an alert and requires an immediate notification and sampling for confirmation[10].

Outbreak threshold: One lab confirmed case is an outbreak[10].

Case Definitions: This sensitive case definition will capture acute Poliomyelitis but also other diseases, including Guillain-Barre syndrome, transverse myelitis and traumatic neuritis, such that each case must be investigated carefully.

Suspected Case: Sudden onset of weakness and floppiness in a child aged <15 years, including Guillain-Barre Syndrome; OR Any paralytic illness in a person of any age whom Polio is suspected by a physician[11].

Polio-compatible AFP: Clinically compatible with Poliomyelitis, but without adequate virological investigation[11].

Confirmed AFP: Laboratory-confirmed wild Poliovirus in stool sample[11].

Discarded case: Discarded case is an AFP case, which is neither diagnosed as confirmed nor compatible with a Polio case definition[11].

Specimen Collection & Transportation: Collect 2 stool samples about 8 grams each (about the size of the tip of both thumbs) at an interval of 24 to 48 hours for virus isolation as soon as possible or within 14 days of onset of illness in a clean, leak proof, screw- capped container, preferably in a transport medium like Minimal Essential Medium or Eagle's Medium. Seal the container with tape and place samples immediately after collection in refrigerator at 2-8°C or in a cold box with frozen ice packs. Transport specimens to the lab maintaining cold chain with duly filled request form within 72 hours after collection. The set of specimens from a single patient should be placed in a single plastic bag just large enough to hold both the containers[12].

Prevention and Control: Four pillars of Polio eradication

- Achieving a high level of coverage with at least 4 doses of the oral Poliovirus vaccine (OPV) and one dose of IPV
- Providing supplementary doses of OPV to all children<5years old during NIDs and SNIDs
- Active and passive surveillance for all cases of acute flaccid paralysis
- House-to-house OPV campaigns, targeting areas in which transmission of wild Poliovirus persists, based on surveillance data[13].

References:

References are available in online version at www.nih.org.pk

Typhoid and Paratyphoid Fever

Introduction:

Typhoid fever, also known as enteric fever is a potentially severe and occasionally life-threatening febrile illness, occurs predominantly in association with poor sanitation and lack of clean drinking water. It is estimated that approximately 21 million cases and 222,000 typhoid-related deaths occur annually worldwide. More than 80% of reports of typhoid fever and >90% of reports of paratyphoid fever caused by Salmonella Paratyphi A are of travelers to southern Asia. Pakistan is located in highly endemic region and incidence rate is 451.7 per 100,000 persons per year of typhoid fever[1].

Clinical Picture: The acute illness is characterized by prolonged high grade fever, headache, nausea, loss of appetite, and constipation or diarrhea. Symptoms are often non-specific and clinically non-distinguishable from other febrile illnesses. Complications include intestinal ulceration and perforation in 3rd week of illness. Typhoid and Paratyphoid fever can rarely result in death among untreated cases[2].

Infectious Agent:

- Typhoid fever: *Salmonella typhi*
- Paratyphoid fever: *Salmonella paratyphi* A, B or C

Reservoir: Humans are the only reservoir for Salmonella typhi, whereas *Salmonella paratyphi* also has animal reservoirs[2].

Mode of Transmission: Faecal-oral route, particularly ingestion of water and food contaminated by faeces and urine of patients and carriers[2].

Incubation Period: Ranges from 8-14 days but may be from 3 days up to 2 months[2].

Period of communicability: The disease is communicable for as long as the infected person excretes *S. typhi* in their excreta, usually after the 1st week of illness through convalescence. Approximately 10% of untreated cases will excrete *S. typhi* for 3 months and between 2-5% of all cases become chronic carriers.

Seasonality: April to August/Monsoon season[1].

Alert Threshold: One confirmed case is an alert[3].

Outbreak threshold: clinically suspected/confirmed cases per 50,000 population[3].

Case Definitions:

Suspected Cases: Any person with acute illness and fever of at least 38°C for 3 or more days with abdominal symptoms; diarrhoea, constipation, abdominal tenderness, prostration and relative bradycardia[3].

Probable Case:

- A suspected case with a positive sero-diagnosis or antigen detection test but no *S. typhi* isolation OR
- A clinical compatible case that is epidemiologically linked to a confirmed case in an outbreak[3].

Confirmed Case: A suspected/probable case that is laboratory confirmed by: Isolation of *Salmonella typhi* from blood, stool or urine specimens[3].

Chronic Carrier: An individual excreting *S. typhi* in the stool or urine for longer than one year after the onset of acute typhoid fever. (1-5% of patients, depending on age, become chronic carriers harboring S.typhi in the gallbladder)[3].

Lab confirmation:

- Gold standard tests are: Blood and bone marrow cultures.
- Serological tests (typhidot/widal) can be done in emergency and outbreak situations but are not considered specific and sensitive

Specimen Collection:

Blood:

- Collect 10-15 ml of blood from school children and adults in order to achieve optimal isolation rates; 2-4 ml is required from toddlers and preschool children.
- For blood culture inoculate media at the time of drawing blood. Once specimens are inoculated, blood culture bottles should not be kept cold. They should be incubated at 37°C or in tropical countries, left at room temperature, before being processed in the laboratory.

Serum: Collect 1-3 ml of blood inoculated in a tube without anticoagulant for serological purposes.

Stool: Collect stool sample in a sterile wide-mouthed plastic container from acute patients, which is useful for the diagnosis of typhoid carriers[4].

Timings: First sample should be collected at the time of presentation and a second sample, if possible, should be collected at the convalescent stage, at least 5 days later[4].

Storage:

Blood: Culture bottles should be inoculated at 37°C/ room temperature in tropical countries.

Serum:

- Separate serum after clotting and store in aliquots of 200 ml at +4°C.
- Testing can take place immediately or storage can continue for a week without affecting the antibody titer.
- For longer storage the serum may be frozen at -20°C[4].

Stool for culture: Specimens should preferably be processed within two hours after collection. If there is any delay, then stored at 4°C or in a cool box with freezer packs[4].

Packaging & Transportation:

- Blood culture bottles should be transported to the referral laboratory as soon as possible.
- Rectal swabs inoculated into Carry Blair transport medium.
- Properly packed (Triple Packaging) and should be transported to the lab in a cool box[4].

Case Management:

Treatment Typhoid Fever:

- Treatment of enteric fever has been complicated by the development resistance to Ampicillin, Trimethoprim-Sulfamethoxazole, and chloramphenicol hence these are no longer considered as first-line agents.
- Fluoroquinolones are recommended for empiric treatment in adults, but quinolone resistance is >80% for Typhi and Paratyphi A infections.
- Injectable third-generation Cephalosporins are often the empiric drug of choice when the possibility of Fluoroquinolone resistance is high.
- Azithromycin and ceftriaxone are increasingly used to treat because of the emergence of multidrug-resistant strains, although increasing resistance to azithromycin has also been documented.
- Ceftriaxone in shortened courses of 5 or 7 days has significant relapse rates.
- Oral Cefixime can be used in Pediatric patients at a dose of 10 mg/kg/day is safe and effective choice.
- If fever in a person with culture-confirmed typhoid does not subside within 5 days, alternative antimicrobial agents or other foci of infection such as abscesses, bone or joint infections, and other extra-intestinal sites should be considered.

Supportive Care: Oral or intravenous rehydration, antipyretics and appropriate nutrition also play an important role[3].

Preventive measures & vaccination:

General Preventive measures:

- Avoiding contaminated food and water, raw vegetables and fruits

that can't be peeled off. Avoiding half cooked foods.

- Typhoid vaccination (vaccines are not recommended in children under 2 years of age)[4].

Preventive Measures during outbreaks: Outbreaks may occur through person-to-person contamination (Faecal-oral transmission via contaminated hands or instruments), and direct feacal contamination of untreated water.

Note: Investigations must pinpoint the source and mode of infection to identify corrective measures for application (Chlorination/boiling of water, selective elimination of suspected food).

- Inform the health authorities if one or more suspected cases are identified.
- Confirm the outbreak.
- Confirm the diagnosis and ensure prompt treatment.
- Mass immunization during sustained, high incidence epidemics[4].

Advisory link: http://nih.org.pk/wp-content/uploads/2018/06/Typhoid-Advisory.pdf

References:

References are available in online version at www.nih.org.pk

VIRAL HEPATITIS A&E

Introduction:

Acute viral hepatitis is a diffuse liver inflammation caused by specific hepatotropic viruses that have diverse modes of transmission. Hepatitis A and E infections are endemic in Pakistan. Both infections occur in their sporadic form due to poor water and sewage systems[1].

Clinical Picture: Acute jaundice, dark urine, anorexia, malaise, extreme fatigue and right upper quadrant tenderness. Biological signs include increased Urobilinogen and >2.5 times the upper limit of serum Alanine Aminotransferase. A variable proportion of adult infections remain asymptomatic[2].

Infectious Agent:

- *Hepatitis viruses A* (HAV)
- *Hepatitis viruses E* (HEV)[3]

Reservoir: Humans are the only reservoir of the Hepatitis A virus humans and non-human primates are the reservoir of Hepatitis E[3].

Mode of transmission: Faecal-oral route[3]

Incubation period:

Hepatitis A: Average 28-30 days, ranges from 15 to 50 days.

Hepatitis E: Range is 15-64 days[3].

Seasonality: Occur regularly during monsoon rains and floods due to major contamination of drinking water with sewage[4].

Alert threshold: 3 or more cases in one location[4].

Outbreak threshold: 6 or more cases in one location and lab confirmation of type of virus[4].

Case Definitions:

Suspected Case: A case that meets the clinical case definition[4].

Confirmed Case: A case that meets the clinical case definition AND is laboratory confirmed.

OR

A case compatible with the clinical description who has an epidemiological link (i.e. household) with a laboratory- confirmed case of Hepatitis A/E during the 15-50 days before the onset of symptoms[4].

Lab confirmation:

- Hepatitis A: Positive for IgM anti-HAV
- Hepatitis E: Positive for IgM anti-HEV (PCR) Polymerase chain reaction[5]

Specimen Collection: Collect 5 ml blood during acute phase of illness observing all safety precautions. Separate serum by centrifugation technique in a tube.

Timings: Pack the specimens and send overnight.

Packaging: An insulated box with ice or frozen refrigerant packs Storage and Transportation: Can be stored at 2-8°C for 48-72 hours. For long term storage, keep at -20° C. Transport in triple package with complete lab request form[4].

Case Management: There is no specific management for acute uncomplicated Hepatitis but general supportive measures are recommended like bed rest, fluid replacement, nutritional support, and avoidance of all the hepatotoxic drugs during the illness. Regarding Hepatitis E, hospitalization is required for fulminant Hepatitis and should be considered for infected pregnant women[4].

Preventive measures: Control procedures for Hepatitis A and E, epidemic-prone diseases, should include provision of safe drinking water and proper disposal of sanitary waste. Good personal hygiene including frequent and proper hand washing after bowel practices and before food preparation, avoiding drinking water and/or ice of unknown purity and avoiding eating uncooked vegetables and unwashed fruits that are not peeled. High quality standards for public water supplies and proper disposal of sanitary waste are important measures to reduce the risk of disease transmission[6].

Vaccination: Hepatitis A vaccine is available both for adults and children aged 2 years or older and is administered intramuscular with a recommended vaccination schedule of 0, 1, and 6-12 months apart. At present, Hepatitis E vaccine is available in China only[4].

References:

References are available in online version at www.nih.org.pk

DENGUE FEVER

Introduction:

Dengue is a mosquito-borne viral disease (also known as break bone fever), causes flu-like illness, and occasionally develops into a potentially lethal complication called severe Dengue. The global incidence of Dengue has grown dramatically in recent decades and about half of the World's population is now at risk[1]. The first confirmed outbreak of Dengue fever in Pakistan was in 1994, but a sudden rise in cases and the annual epidemic trend first occurred in Karachi in November 2005[2].

Clinical Picture:

Dengue Fever: Dengue fever is defined by fever (for>3 days and <10days) as reported by the patient or healthcare provider and the presence of one or more of the following signs and symptoms i.e. nausea/vomiting, rash, aches and pains (e.g., headache, retro-orbital pain, joint pain, myalgia, arthralgia), tourniquet test positive, Leukopenia (Platelets count <150,000).

Dengue Hemorrhagic Fever: Defined as Dengue fever with any one or more of the warning signs i.e. severe abdominal pain or persistent vomiting, red spots or patches on the skin, bleeding from the nose or gums, blood in vomiting, black tarry stools (feces, excrement), drowsiness or irritability, pale, cold or clammy skin, difficulty in breathing, a total white blood cells count of <50,000/mm3 and Platelets count <100,000.

OR

Dengue Shok Syndrome: Defined as Dengue fever with any one or more of the following scenarios:

Severe plasma leakage evidenced by hypovolemic shock and/or extravascular fluid accumulation (e.g., pleural or pericardial effusion, ascites) with respiratory distress, severe bleeding from the gastrointestinal tract and vital organs involvement[3].

In 1-3% of cases, the disease develops into the life-threatening Dengue hemorrhagic fever (DHF), sometimes progressing into Dengue shock syndrome (DSS)[4].

Infectious Agent[5]: Belonging to *Flavivirus* group; four different

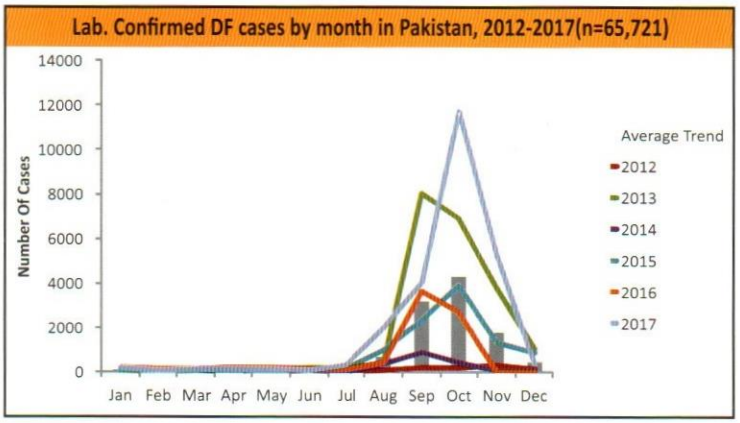
Dengue viruses (serotypes) are known: *DEN1, DEN2, DEN3, and DEN4.*

Mode of transmission: Bite of infected mosquitoes, Aedes Aegypti and Aedes Albopictus[6].

Incubation period: 3-14 days (average 4–7 days) after the infective bite[7].

Period of communicability: 2–7 days[7].

Seasonality: Cases are increased during and after rainy seasons as compared to winter and summer seasons. Relatively humidity, temperature and rain remained significant predictors of dengue incidence in Pakistan. Surge of cases occurred during September to October[8].

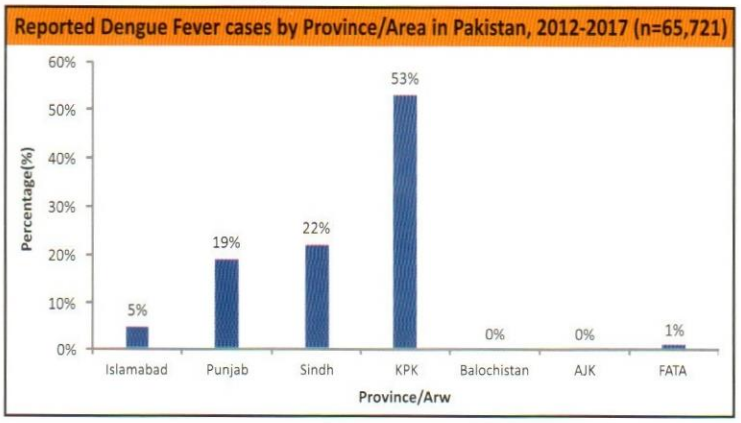


Geographical distribution: During 2012-2016, KP remained most affected area with Dengue Fever in Pakistan.

Alert Threshold: Dengue Fever: Cluster of 3 suspected cases with at least one confirmed[10].

Alert Threshold; Dengue Haemorrhagic Fever:

One probable case is an alert and requires an immediate investigation to assess differential diagnosis with CCHF.



Outbreak threshold: Cluster of 6 suspected cases and one lab confirmed case is an outbreak[10].

Case Definitions:

Suspected Case: A clinically compatible case of Dengue fever, or Dengue hemorrhagic fever with an epidemiologic linkage[11]

Probable Case: A clinically compatible case of Dengue fever, or Dengue hemorrhagic fever with laboratory results indicative of probable infection[11]

Confirmed Case: A clinically compatible case of dengue fever, or Dengue hemorrhagic fever with confirmatory laboratory results[11].

Lab Confirmation:

Probable; Detection of IgM anti-DENV by validated immunoassay in a serum specimen

Confirmatory Test:

Detection of DENV nucleic acid in serum/plasma by PCR, detection in serum or plasma of DENV Non Structural Protein[1] (NS1) antigen by a validated immunoassay

Timings:

PCR: Initial 4–5 days of onset of illness.

NS1: One day post onset of symptoms (DPO) up to 18 DPO

Serology:

IgM antibodies are detectable after 4th day of onset of illness IgG is used for the detection of past dengue infection and usually can be detected during 2nd week of illness[11].

Specimen Collection and Transportation:

Collect 5 ml of blood, centrifuge, and separate serum for analysis, observing strict safety precautions. Transport serum specimens to the lab in triple container packing with ice packs or frozen with dry ice (for long distance) along with a prominent bio hazard label and complete lab request form with brief history of the patient[10].

Case Management:

Febrile Phase: In the early febrile phase, it is not possible to distinguish DF from DHF. The treatment during febrile phase is symptomatic and largely supportive, as follows:

Paracetamol 10 mg/kg/dose in children and 500-1,000 mg/dose in adult. Maximum adult dose is 4 grams/day. Do not give Aspirin or other NSAID like Ibuprofen.

Extra amounts of fluids Oral rehydration therapy (ORT/ ORS) is recommended for patients with moderate dehydration .Complete blood count (CBC/CP) with follow up is an important tool in management of suspected dengue patients .Provide brochure for families about the "warning signs" together with other recommendation. All Dengue patients must be carefully observed for signs of shock for at least 24 hours after recovery from fever.

The patient who does not have any evidence of circulatory disturbance and who has been afebrile for > 24 hours does not need further observation and may be discharged[10].

Protocol for management according to Phases of DHF

(1) Dengue hemorrhagic fever (DHF) Grades I and II:

As in DF, during the afebrile phase of DHF Grades I and II, the patient has the same symptoms as during the febrile phase. The clinical signs plus thrombocytopenia and rise in hematocrit are sufficient to establish a clinical diagnosis of DHF. During this situation hospitalize the patient and treat accordingly.

(2) DHF Grades III and IV (DSS):

Common manifestations observed during the afebrile phase of DHF Grade III are circulatory failure manifested by rapid and weak pulse, narrowing of the pulse pressure characterized by high diastolic pressure relative to systolic pressure, e.g. 90/80 mm of Hg (this is usually due to plasma leakage) or hypotension (possibly due to bleeding), the presence of cold clammy skin and restlessness or lethargy. Immediately shift the patient to Intensive care unit (ICU) and treat accordingly. The mortality is up to 30% without treatment but less than 1% with adequate treatment by experienced physician in dedicated facility[10].

Preventive Measures:

Community survey to determine density of vector mosquitoes Identify and destroy mosquito larval habitats and indoor breeding sites. Community mobilization should be conducted through schools, religious leaders, to promote health education campaigns.

Proper solid waste disposal and improved water storage practices, including covering containers to prevent access by egg-laying female mosquitoes. Protection against day biting mosquitoes including use of screening, protective clothing and repellents[10].

Vaccination:

In late 2015 and early 2016, the first Dengue vaccine,Dengvaxia(CYD-TDV) was registered in several countries for use in Individuals aged 9-45 years living in endemic areas[12]. WHO recommends that countries

should consider introduction of the Dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease[13].

References:

References are available in online version at www.nih.org.pk

Malaria

Introduction:

Malaria is a vector borne parasitic disease transmitted by female Anopheles mosquito species1. With an estimated one million cases annually, Pakistan remains one of the highest Malaria burden sharing countries in WHO-EMRO, and has been grouped with Sudan, Yemen, Somalia and Afghanistan. An estimated 98% of Pakistan population (185 million) is at varying risk for Malaria, while population at high risk is around 29% (54.6 million). The highest endemic districts/agencies are located in bordering regions with Iran and Afghanistan. Every year >3.6 million Malaria suspects are treated as Malaria cases in health facilities without confirmatory tests[2].

Clinical Picture: Fever, chills, sweats, headache, nausea and vomiting, body aches and general malaise[3].

Un-complicated: The classical (but rarely observed) Malaria attack lasts 6-10 hours. It consists of:

- Cold stage (sensation of cold, shivering),
- Hot stage (fever, headaches, vomiting; seizures in young children),
- Sweating stage (sweats, return to normal body temperature, tiredness).

Classically (but infrequently observed) the attacks occur every second day with the "tertian" parasites (P. falciparum, P. vivax, and P. ovale) and every third day with the "Quartan" parasite (P. malariae)[3]

Complicated:

- Cerebral malaria, with abnormal behavior, impairment of consciousness, seizures, coma, or other neurologic abnormalities
- Severe anemia due to hemolysis
- Hemoglobinuria
- Acute respiratory distress syndrome (ARDS)
- Abnormalities in blood coagulation
- Low blood pressure caused by cardiovascular collapse
- Acute kidney failure
- Hyperparasitemia, where more than 5% of the red blood cells are infected by Malaria parasite
- Hypoglycemia[3]

Infectious Agent:

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*
- *Plasmodium knowlesi* (rarely infect humans)[4]

Note: *Plasmodium falciparum and Plasmodium vivax* are the most prevalent species are prevalent in Pakistan.

Reservoir: Humans are the only known reservoir[4]

Mode of Transmission:

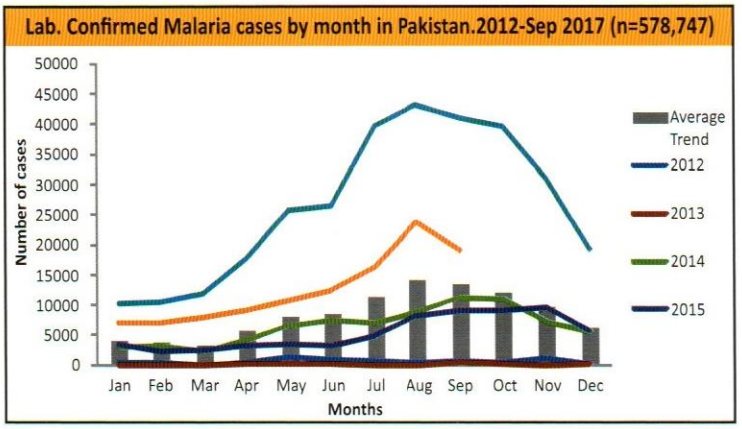
Bite of an infective female Anopheles mosquito and rarely through blood transfusion from an infected person

Incubation period: P. falciparum 9-14 days, P.malarie 18-40 days, P. ovale and P. vivax 12-18 days[4]

Infectivity:

Humans may infect mosquitoes as long as infective gametocytes are present in the blood. Anopheles mosquitoes remain infective for life[4]

Seasonality: Peaks occur during rainy season (August-September)[5]



Alert threshold:

Number of cases reaches two times the mean number of suspected cases of the previous 3 weeks for a given location[6].

Outbreak threshold:

In endemic areas: Slide positivity rate above 50% or falciparum rate above 40%; while in non-endemic areas, evidence of indigenous transmission of falciparum[6].

Case Definitions:

Suspected Case: A case with clinical manifestations of uncomplicated/complicated Malaria[6]

Probable Case: A suspected case with history of similar manifestations among other household members[6]

Confirmed Case: Clinical case with laboratory confirmation[6]

Lab Confirmation:

- Peripheral blood smear (gold standard for identification of Malarial parasite, trophozoites and gametocytes, within RBCs)
- Rapid Diagnostic Test (Immunochromatography)
- PCR
- Serology (Indirect immunofluorescence and ELISA)

Note: Not for diagnosis of current infection; screening of blood donors, previously treated with questionable diagnosis and testing the patient from endemic area having recurrent / chronic Malaria infection

Specimen Collection & Transportation:

Peripheral Blood Film: Collect 3-5ml blood in a tube with anticoagulant (EDTA).

Immunodiagnostic test kit: Sample may also be used to demonstrate parasite antigen. Transport the specimen at room temperature preventing sample spillage or damage to the tubes[6]

Case Management

Warning: Do not give Primaquine to pregnant women and children <2 years of age and it is advisable to do a Glucose-6-phosphate dehydrogenase (G6PD) test before giving this drug. Give Primaquine preferably after the patient has recovered from the acute illness.

- Do not give undiluted Chloroquine or Quinine by I/M or I/V route, as it can cause sudden cardiac arrest, especially in children
- Do not give Sulfadoxine/ Pyrimethamine to children <2 months of age or during first trimester of pregnancy
- Suspected/probable case of severe Malaria and high risk groups should be treated immediately[6].

Treatment of uncomplicated Falciparum Malaria

Artemisinin-based combination therapies (ACTs) are the recommended treatments for uncomplicated P. falciparum Malaria. However, Artemisinin and its derivatives should not be used as monotherapy. The following ACTs are recommended:

- Artesunate plus Sulfadoxine-
- Pyrimethamine Artemether plus lumefantrine,

- Artemether-lumefantrine is currently available as a fixed-dose formulation with dispersible or standard tablets containing 20 mg of Artemether and 120 mg of lumefantrine. The recommended treatment is a 6-dose regimen twice Daily (BD) over a 3-day period. The dosing is based on the number of tablets per dose according to reported AWD cases by month in Pakistan, pre- defined weight bands (5–14 kg: 1 tablet; 15–24 kg: 2 tablets; 25–34 kg: 3 tablets; and > 34 kg: 4 tablets)
- In case of pregnant women, during first trimester Quinine plus Clindamycin to be given for 7 days (Artesunate plus Clindamycin for 7 days is indicated if this treatment fails[6].

Uncomplicated Vivax Infections

Chloroquine combined with Primaquine is the treatment of choice for Chloroquine-sensitive infections. Dosage is as given below:

- Chloroquine: 04 STAT, 02 after 6 hours, then 12 hourly for 02 days.
- Primaquine: 0.25mg/kg body weight daily for 14 days treatment is prescribed for radical treatment of Vivax[7].

Preventive Measures:

Travelers and their advisers should note the four principles – the ABCD –of malaria protection:

- Be Aware of the risk, the incubation period, the possibility of delayed onset, and the main symptoms.
- Avoid being bitten by mosquitoes, especially between dusk and dawn.
- Use antimalarial dugs (Chemoprophylaxis) when appropriate, to prevent infection from developing into clinical disease.
- Immediately seek diagnosis and treatment if a fever develops one week or more after entering an area where there is a Malaria risk and up to 3 months (or, rarely, later) after departure from a risk area[8].

a) Personal protection

- Wear long sleeves and trousers outside the houses during the evening. Use repellent creams and sprays. Avoid of night time outside activities.
- Use mosquito's coils or vaporizing mat containing a Pyrethrin.
- Use of Insecticide-treated mosquito nets (ITNs)

b) Vector control

- Indoor spraying with residual insecticides (IRS)
- Reduce mosquito breeding sites
- Improve vector surveillance

c) Chemoprophylaxis Malaria control Program:

Recommended chemoprophylaxis: Atovaquone-proguanil, Doxycycline or Mefloquine[8]

References:

References are available in online version at www.nih.org.pk

Potential National Public Health Events

Primary Amebic Meningoencephalitis (PAM)

Introduction: Since the detection of the first case in Australia during 1965; about 300 cases have been reported from 16 countries. In Pakistan since 2012, a total of 45 fatal cases have been reported from different tertiary care hospitals of Karachi including 3 fatal case during 2018. It is caused by the parasite Naegleria fowleri; a rare disease, with about 99% CFR. Naegleria fowleri (brain-eating amoeba) is a unicellular, free-living microscopic & grows best at higher temperature up to 46°C & is naturally found in warm freshwater environments feeding on bacteria and other microbes. Transmission occurs primarily through inhalation of infested water during swimming/bathing during ablution from untreated municipal water, untreated well water, untreated swimming pools and spas, as well as in warm lakes and mud puddles. Symptoms start 1-9 days (median 5 days) after nasal exposure to Naegleria-containing water. People may die 1-18 days (median 5 days) after symptoms occur. Transmission does not occur by drinking contaminated water or by swimming in sea. Initial symptoms of PAM usually start from 1-7 days after infection which may include headache, fever, nausea or vomiting.

Clinical Manifestations: Similar to bacterial meningitis (severe frontal headache, fever, vomiting, meningeal signs, stiff neck, seizures and focal neurologic deficits) that increases chances of misdiagnosis. After the onset of symptoms, the disease progresses rapidly and while death may occur in 1-12 days of illness. The diagnosis is usually made after death due to the rapid progression of the disease.

Control: Both trophozoites and cysts forms are sensitive to adequate levels of chlorination. The municipality public health authorities therefore, must ensure that adequate levels of disinfectants like chlorine are maintained in the supplied tap water along with strict monitoring arrangements. Any of the suspected cases should immediately be reported to health authorities. Awareness and education in the affected areas must also be undertaken to educate people on requisite preventive measures.

Prevention: Avoid water activities in pools, ponds and water or untreated water, keep head above water or use a nose clip when the water is warm or the temperature is near or above 80°F (about 27°C), use distilled, sterile, or previously boiled and cooled water for nasal rinses; (less likely to be practical than chlorination) and periodic cleaning of water tanks and chlorinating water.

Salmonella enterica serovar typhi (extensively drug resistant strain)

Introduction: *Salmonella enterica serovar typhi* causes typhoid fever, a life-threatening illness that affects more than 21 million people in the developing world. The bacterium is transmitted by contaminated water and food and tends to spread in areas with poor sanitation.

Antibiotic resistance is a major problem in Salmonella typhi. Multidrug-resistant (MDR) isolates are prevalent in parts of Asia and Africa and are associated with the dominant H58 haplotype. Reduced susceptibility to Fluoroquinolones is also widespread, and sporadic cases of resistance to third-generation Cephalosporins or Azithromycin have also been reported.

In Pakistan the first large-scale emergence and spread of a novel S. typhi clone harboring resistance to three first-line drugs (Chloramphenicol, Ampicillin, and Trimethoprim-Sulfamethoxazole) as well as Fluoroquinolones and third-generation Cephalosporin has been identified in Sindh, which was classified as extensively drug resistant (XDR) .Whole-genome sequencing of 87 of the 339 XDR Salmonella typhi strains isolated from November 2016 to March 2017 from the Sindh region, primarily in the cities of Karachi and Hyderabad. Additionally, a single case of travel-associated XDR typhoid has recently been identified in the United Kingdom

Clinical manifestations: Patient presents with history of high grade fever (103°F to 104°F), Weakness, Stomach pains, headache, loss of appetite, in some cases, patients have a rash of flat, rose-colored spots.

Blood complete picture and Blood/ stool/ urine cultures are performed to confirm the diagnosis of typhoid fever.

Preventive measures and control:

- Along with the appropriate treatment, preventive measures are urgently needed, including improved sanitation, food safety and vaccination.
- The antibiotic resistance strains have been treated patients with Azithromycin and Meropenem.
- Typbar-TCV vaccine, a trivalent conjugate vaccine that was recently prequalified by the World Health Organization is recommended. The vaccine has long-lasting immunity, requires only one dose, and can be given to children as young as 2 years.

References: *References are available in online version at www.nih.org.pk*

Heat Stroke

Introduction: Heat stroke is a medical emergency and is a form of hyperthermia in which the body temperature elevates dramatically and can be fatal if not promptly and properly treated. The body's temperature rises rapidly, the sweating mechanism fails and the body becomes unable to cool down consequently, the body temperature can rise to 104°F or higher within 10 to 15 minutes.

Signs & Symptoms: It include profuse sweating or the absence of sweating, with hot red or flushed dry skin, weakness/lethargy, chills, throbbing headache, high body temperature, hallucinations, confusion/ dizziness and slurred speech. Heat stroke can cause death or permanent organ damage or disability if not properly treated in time. Infants, elder persons, athletes and outdoor workers are at high risk for heat stroke.

Treatment: Professional medical treatment should be obtained immediately. The most critical step is the lowering of the temperature of the patients. The patients should be moved to shady area, unnecessary clothing should be removed and cool tepid water should be applied to the skin while soaking remaining clothes with water. Notify the emergency services immediately as severe cases often require hospitalization and Intravenous re-hydration. Promote sweat evaporation by placing the patient before fan and ice packs under the armpits and groin. If the patient is able to drink liquids, he/ she should be given plenty of cool water or other cool beverages that do not contain alcohol or caffeine. Maintain intravenous fluids and hospitalize if required. Monitor body temperature with a thermometer and continue cooling efforts until the body temperature drops to 101°F to 102°F. Antipyretics may be given once the body temperature drops to 101°F or below.

Preventive Measures: Drink plenty of water while limiting time in direct sunlight in hot/ humid weather or in places with high environmental temperatures, avoid becoming dehydrated and to refrain from vigorous physical activities. Public should be made aware of early signs/ symptoms of dehydration and subsequent evolving signs and symptoms of heat/ sun stroke such as muscle cramps, nausea, vomiting, light-headedness and even heart palpitations. The patients should avoid use of alcohol and caffeine containing soft drinks and/or tea), which may exacerbate dehydration. Public should be encouraged to consume salty foods, wear hats and light-colored, lightweight and loose clothes during the hot/ humid environmental conditions.

Guidelines link: http://nih.org.pk/wp-content/uploads/2018/05/Heat-SunStroke.pdf

Potential International Public Health Events

Ebola Virus Disease (EVD)

Introduction: Ebola Virus Disease (EVD) is caused by the Ebola virus; with the average case fatality rate is around 50%. Symptoms may appear from 2 to 21 days after exposure which typically include fever, headache, joint and muscle aches, weakness, diarrhea, vomiting, stomach pain and lack of appetite and may be followed by rash, red eyes, difficulty breathing, difficulty swallowing, bleeding from different sites of the body. A person infected with Ebola virus is not contagious until symptoms appear. Ebola cannot spread through the air, food and water. The virus can spread through direct contact with the body fluids of an infected person. No specific drug available however early supportive clinical treatment and management are essential and can improve the chances of recovery. The outbreak of Ebola virus disease began in West Africa mainly affecting Guinea, Liberia and Sierra Leone in Dec-2013 and declared as Public Health Emergency of International Concern (PHEIC) by WHO.

On 8 May 2018, the Ministry of Health (MOH) of the Democratic Republic of the Congo officially declared an outbreak of Ebola virus disease in Bikoro Health Zone, Equateur Province. This is the ninth outbreak of Ebola virus disease over the last four decades in the Democratic Republic of Congo, with the most recent occurring in May 2017. In May 2018, cases erupted from the same area and as of 11 June, there were a total of 59 confirmed, probable and suspected Ebola cases, of which 28 people had died.

Risk assessment: The risk is low at global level due to the remoteness and inaccessibility of the area as well as the rapid response launched by the Democratic Republic of Congo MoH, WHO, and all the other coordinating partners.

Public Health Measures: WHO recommends the implementation of proven strategies for the prevention and control of Ebola Outbreaks. These strategies include (i) coordination of the response, (ii) enhanced surveillance, (iii) laboratory confirmation, (iv)contact identification and follow-up, (v) case management, (vi) infection prevention and control, (vii) safe and dignified burials, (viii) social mobilization and community engagement, (ix) logistics, (x) risk communication, (xi) vaccination, (xii) partner engagement, (xiii) research and (xiv) resource mobilization.

Guidelines link: hp://nih.org.pk/files/Guidelines/Recommended%20Standard.pdf

Nipah Virus (NiV)

Introduction: It is an emerging Zoonosis that causes severe disease in both animals and humans and endemic in South-East Asia Region. NiV was initially isolated and identified in 1999 during an outbreak of encephalitis and respiratory illness among pig farmers and people with close contact with pigs in Malaysia and Singapore. Nipah capable of causing severe disease in pigs and other domestic animals.

Clinical Picture: Encephalitis: fever and headache, followed by drowsiness, disorientation and mental confusion. These signs and symptoms can progress to coma within 24-48 hours. Some patients have a respiratory illness/Influenza like Illness.

Long-term squeal following Nipah virus infection have been noted, including persistent convulsions and personality changes.

Diagnosis & Specimen Collection: Diagnostic methods include RT-PCR, Serological testing by (IgG and IgM by ELISA), Virus Isolation, Histopathology and Immunohistochemistry (IHC) on tissues collected. For PCR throat and nasal swabs, cerebrospinal fluid, urine and blood & for Serology at least 5 ml of serum is required.

Packaging and Transportation: Tissues were either fixed in 10% neutral buffered formalin for 48 h prior to histological processing or submerged in RNA or viral transport medium and then stored at −80°C until processing, respectively. It is transported by viral medium.

Treatment & Preventive Measures: Treatment is mostly focused on managing fever and the neurological symptoms. Supportive Care. Ribavirin may alleviate symptoms of nausea, vomiting and convulsions. (Limited data available).

Severely ill individuals need to be hospitalized and may require use of ventilator. No vaccination for human use is available. It can be prevented by avoiding exposure to sick pigs and bats in endemic areas and not drinking raw date palm sap. Raising public awareness of transmission and symptoms is important in reinforcing standard infection control practices to avoid human-to-human infections in hospital setting.

Guidelines link: http://nih.org.pk/wp-content/uploads/2018/06/Nipah.pdf

Middle East Respiratory Syndrome Coronavirus (MERS - CoV)

Introduction: First reported case was from Saudi Arabia in September 2012. So far, all cases of MERS have been linked through travel to or residence in countries in and near the Arabian Peninsula. MERS is viral respiratory illness caused by corona virus from the same family which caused outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003. The source of the virus remains unknown but virological studies point towards dromedary camels. MERS-CoV has spread from ill people to others through close contact, such as caring for or living with an infected person. Incubation period is 1-2 weeks. The clinical presentation of MERS ranges from asymptomatic to very severe pneumonia with acute respiratory distress syndrome, septic shock and multi-organ failure resulting in death. The clinical course is more severe in immune-compromised patients and persons with underlying chronic co-morbidities. Human-to-human transmission has occurred mainly in health care settings. Since April 2012, a total of 2,220 cases of MERS, including 790 deaths have been reported from 27 countries worldwide (Algeria, Austria, Bahrain, China, Egypt, France, Germany, Greece, Islamic Republic of Iran, Italy, Jordan, Kuwait, Lebanon, Malaysia, the Netherlands, Oman, Philippines, Qatar, Republic of Korea, Saudi Arabia, Thailand, Tunisia, Turkey, UAE, UK, USA and Yemen).

Sample Collection and Transportation: Collection of lower respiratory specimens (sputum or broncho-alveolar lavage) is strongly recommended however, nasopharyngeal swab, oropharyngeal swab, sputum, serum, and stool/rectal swab may be collected. Repeat sequential sampling for PCR testing is strongly encouraged in the respiratory tract (upper and lower) and multiple other body compartments. Wear personal protective equipment and adhere to infection control precautions and notify to district health departments if suspect MERS-CoV infection in a person.

Treatment and Prevention: No specific treatment/ drugs and vaccines are currently available. Treatment is mainly supportive and based on the clinical condition of the patient. Preventive measures include standard plus aerosol, droplet precautions and practicing good hand hygiene.

Guidelines link: http://nih.org.pk/wp-content/uploads/2018/01/Guidelines-for-the-Prevention-Control-and-Management-of-Middle-East-Respiratory-Syndrome-Coronavirus-MERS-CoV-updated-MAY-2014.pdf

Yellow Fever

Introduction: Yellow fever is caused by a virus *(Flavivirus)* which is transmitted to humans by the bites of infected Aedes and haemogogus mosquitoes. Occasionally, infected travelers from areas where yellow fever occurs have exported cases to other countries.

Sign & Symptoms: The first symptoms of the disease usually appear 3–6 days after infection. The first, or "acute", phase is characterized by fever, muscle pain, headache, shivers, and loss of appetite, nausea and vomiting. After 3–4 days, most patients improve and symptoms disappear. However, in a few cases, the disease enters a "toxic" phase: fever reappears, and the patient develops jaundice and sometimes bleeding, with blood appearing in the vomit. About 50% of patients who enter the toxic phase die within 10–14 days.

Disease Burden: According to a recent analysis, an estimated 84,000–170,000 cases and up to 60,000 deaths occur due to yellow fever per year. The virus is endemic in tropical areas of Africa and Latin America. Between January 2016 and January 2018, seven countries and territories of the Region of the Americas reported confirmed cases of yellow fever: the State of Bolivia, Brazil, Colombia, Ecuador, French Guiana, Peru, and Suriname. Since the 12th January 2018 Epidemiological Update on Yellow Fever published by the Pan American Health Organization / World Health Organization (PAHO/WHO), Brazil and Peru had reported new yellow fever cases. In Brazil, between 1 July 2017 and 15 February 2018,

there were 409 confirmed human cases of yellow fever, including 118 deaths. In Peru, between epidemiological week 1 and 4 of 2018, three probable cases of yellow fever were reported, one of which was confirmed by laboratory. All 3 cases had no history of yellow fever vaccination.

Yellow fever has never been reported from Pakistan but there are vulnerabilities for importation and its transmission through the presence of vector mosquito (Aedes Aegypti), warm humid environment, susceptible hosts and movements of ships, containers, aircrafts and international travelers. Unvaccinated travelers heading to areas with active yellow fever outbreaks pose a risk of introducing the virus into areas where yellow fever risk factors (human susceptibility, prevalence of competent vector, and animal reservoirs) are present.

Recommendations:

- Ensuring the acceleration of surveillance, vaccination for travelers, risk communications, community mobilization, vector control, quick development of diagnostic capacity and case management measures must be in place. Blood tests to detect yellow fever-specific IgM antibodies or virus genome by PCR must be conducted by a highly trained laboratory staff with specialized equipment and materials.
- There is no specific treatment for yellow fever except supportive care. Yellow fever can be prevented through vaccination and mosquito control. WHO recommends vaccination for all travelers older than 9 months of age in areas where there is evidence of persistent or periodic yellow fever virus transmission
- Centers for Disease Control and Prevention (CDC) updated their travel notice for Brazil. Travelers to Brazil should protect themselves from yellow fever by getting yellow fever vaccine at least 10 days before travel, and preventing mosquito bites.

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