Ministry of National Health Services, Regulations & Coordination
Government of Pakistan
National Institute of Health, Islamabad, Pakistan
Centers for Disease Control (CDC) (Ex-FE&DSD),
Tel: 051-9255237, 9255575
National Focal Point for International Health Regulations (IHR)

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SEASONAL AWARENESS AND ALERT LETTER (SAAL)

For Epidemic-prone infectious diseases in Pakistan

Winter Season

OBJECTIVES OF SAAL

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

DATA SOURCES

- The available national data collected during 2016 to 2022 by CDC (Ex-FE&DSD), NIH, Provincial Health Departments, Provincial Disease Surveillance & Response Units (PDSRUs), Expanded Program on Immunization (EPI), Directorate of Malaria Control and laboratory-based data from NIH has been analyzed to assess the exhibited patterns of high priority communicable infectious diseases.
- The description of all priority diseases has been arranged in an alphabetical order. Additionally, under the section of National Potential Public Health Events, technical detail on the Human Immunodeficiency Virus (HIV)is included. Ebola Virus disease has been shared as an International Public Health Event.

Outbreak - Prone Diseases	Alerts
Coronavirus Disease 2019 (COVID-19)	
Crimean Congo Hemorrhagic Fever (CCHF)	
Dengue Fever	
Gastroenteritis (Acute)	
Leishmaniasis	
Malaria	
Measles	
Meningococcal Meningitis	
Pertussis	
Poliomyelitis	
Probable Diphtheria	
Seasonal Influenza	
Typhoid Fever (XDR)	

High Alert- peak occurrence in the Summer/Monsoon season

Medium Alert- cases will be encountered and may show up as an outbreak

Coronavirus Disease (COVID-19)

Introduction: A Novel Coronavirus Disease (COVID-19) is a member of the coronavirus family that has never been identified or encountered before. Coronaviruses are large family of viruses causing illness in humans as well as among animals i.e. camels, cats and bats. MERS-COV and SARS-CoV-1 belongs to the same family. Coronaviruses are named for the crown-like spikes on their surfaces.

Outbreak of this viral disease started in Wuhan city, capital of central China's Hubei province during late December 2019, when a cluster of patients was admitted to hospitals in Wuhan with an initial diagnosis of pneumonia of unknown aetiology (1). The cluster was epidemiologically linked to a local seafoodand wet animal wholesale market, suggestive of zoonotic spillver. Amid the rising spread of the Novel Coronavirus cases globally, the World Health Organization has declared this infectious disease as Public Health Emergency of International Concern (PHEIC) on January 30, 2020 (2).

COVID-19 cases from 26th Feb 2020 to 4th Dec 2022 in Pakistan:

Number of COVID-19 Lab. confirmed cases	Number of COVID-19 cases recovered	Number of deaths due to COVID-19
1,575,329	1,543,985	30,632

Incubation Period: It ranges from 02 days to 14 days from the date of last contact to infected person.

Seasonality: Not yet known

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

Outbreak Threshold: One lab confirmed case of COVID-19 is an outbreak (7).

Case Definitions Suspected Case: person who meets the clinical AND epidemiological circumstances and settings in which procedures or support treatments that generate aerosols are performed i.e. endotracheal intubation, bronchoscopy, administration of nebulized treatment, turning the patient to the prone position, disconnecting the patient from the ventilator, tracheostomy,

criteria:

Clinical Criteria:

Acute onset of fever AND cough; OR

Acute onset of ANY THREE OR MORE of the following signs or symptoms: Fever, cough, generalized weakness/ fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhoea, altered mental status

AND

Epidemiological Criteria:

- Residing or working in an area with high risk of transmissionof virus, closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons; anytime

within the 14days prior to symptom onset ;or

- Residing or travel to an area with community transmission anytime within the 14daysprior to symptom onset; or
- Working in any health care setting, including within health facilities or within the community ;any time within the 14days prior of symptom onset

Probable case:

A) A patient who meets clinical criteria above AND is a contactof a probable or confirmed case, or linked to a COVID-19 cluster

B) A suspect case with chest imaging showing findings suggestive of COVID-19 disease

C) A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identifiedcause

D) Death, not otherwise explained, in an adult with respiratory distress preceding death AND was a contact of a probable or confirmed case or linked to a COVID-19 cluster

Confirmed case:

A) A person with a positive Nucleic Acid Amplification Test (NAAT)

B) A person with a positive SARS-CoV-2 Antigen-RDT AND meeting either the probable case definition or suspect criteria A OR B

C) An asymptomatic person with a positive SARS-CoV-2Antigen-RDT who is a contact of a probable or confirmed case.

Note: For confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after thedate on which the sample was taken which led to confirmation.(7)

Laboratory Confirmation: Routine confirmation of COVID-19 cases is based on detection of COVID-19 virus nucleic acid (RNA) by real time RT-PCR assays. RNA can be extracted fromsamples such as oropharyngeal/nasopharyngeal swabs, nasal swabs/secretions, bronchoalveolar lavage fluid/washings or sputum, using any standard extraction protocols or kits.

Specimen Collection and Transportation: For transport of samples for viral detection, use viral transport medium (VTM) containing antifungal and antibiotic supplements. Avoid repeated freezing and thawing of specimens. If VTM is not available sterile saline may be used instead (in which case, duration of sample storage at 4 °C may be different from whatis indicated below).

New variants of the virus that causes COVID-19: Viruses constantly change through mutation, and new variants of a virus are expected to occur over time. Multiple variants of thevirus that causes COVID-19 have been documented and circulating globally during this pandemic. These variants seemto spread more easily and quickly than other variants, which may lead to more cases of COVID-19:

- The United Kingdom (UK), identified a variant called B.1.1.7 with a large number of mutations in the fall of 2020. This variant spreads more easily and quickly than other variants. In January 2021, experts in the UK reported that this variant may be associated with an increased risk of death compared to other variant viruses.
- In South Africa, another variant called B.1.351 emerged independently of B.1.1.7. Originally detected in early October 2020, B.1.351 shares some mutations with B.1.1.7.
- In Brazil, a variant called P.1 emerged that was first identified in travelers from Brazil, who were tested during routine screening at an airport in Japan, in early January 2021.
- In India, a new variant named B.1.617 was first detected in late October 2020. Later on, experts have identified three subtypes, or sub lineages: B.1.617.1, B.1.617.2, and B.1.617.3. Infections happen with this variant in only a small proportion of people who are fully vaccinated. Preliminary evidence suggests that fully vaccinated people who do become infected with the Delta variant can spread the viral infection to others.
- The B.1.1.529 variant (WHO label: Omicron) was first reported to WHO from South Africa on 24 November 2021(10). Infection with this variant causes milder symptoms with a very low hospitalization rate in fully vaccinated people.
- All above mentioned variants are prevalent in Pakistan.

Case Management: There is no medication presently approved by the U.S. Food and Drug Administration (FDA) toprevent or treat COVID-19. There is no role of prophylactic chloroquine or hydroxychloroquine at this time. Current case management includes infection prevention & control measures and supportive care, including supplemental oxygenand mechanical ventilatory support when indicated.

Preventive Measures:

1. Clean hands regularly with an alcohol-based hand rub, or wash thoroughly with soap and water.
2. Clean surfaces regularly with recommended disinfectants (70% Ethyl Alcohol or 0.5% bleach solution).
3. Avoid touching eyes, nose and mouth with contaminated hands.
4. Practice respiratory hygiene by coughing or sneezing into a bent elbow or tissue and then immediately dispose off.
5. Wear a medical/surgical mask if you have respiratory symptoms and perform hand hygiene after disposing off ofthe mask.
6. Maintain a minimum of mandatory one meter or three feet distance from individuals with respiratory symptoms.

Vaccination: Vaccination is one of the most effective ways to protect us against COVID-19 and prevent the spread. It is possible that a person could be infected with the virus that causes COVID-19, just before or just after vaccination and then get sick because the vaccine did not have enough time to provide protection or development of antibodies. Sometimes after vaccination, the process of building immunity can cause symptoms, such as fever or mild body aches(10).

COVID-19 Vaccines: There are four types of vaccines recommended against COVID-19 namely; Whole virus vaccine, RNA or mRNA vaccine, Non replicating viral vector and Protein subunit.

In Pakistan: Till date, following 5 vaccines procured and administered are approved by Drug Regulatory Authority of Pakistan (DRAP):

- CanSino Ad5-nCoV (Non replicating viral vector)
- Pfizer BNT16b2 (mRNA)
- Gamaleya Sputnik (Non replicating viral vector)
- Oxford/AstraZeneca AZD1222 (Non replicating viral vector)
- Sinopharm (Beijing) BBIBP-CorV (Whole vaccine; In activated)
- Sinovac CoronaVac (Whole vaccine; In activated)

Note: *COVID-19 is an emerging infectious novel disease and with*

the day to day evolving situation, there is more to learnabout its transmissibility, severity, vaccine development & management and other pertinent features.

Guideline Links:

- https://www.nih.org.pk/novel-coranavirus-2019-ncov/

CRIMEAN-CONGO HEMORRHAGIC FEVER (CCHF)

Introduction: A tick-borne zoonotic viral disease that is asymptomatic in infected animals, but can be a serious threatto humans (1). Human infections begin with non-specific febrile symptoms, but can progress to a serious hemorrhagicsyndrome with a high case fatality rate (10 – 40%) (2). It is one ofthe most widely distributed viral hemorrhagic fevers occurringin different parts of Africa, Middle-East, Asia and Europe. CCHFis endemic in Pakistan with sporadic outbreaks. (3). Occurrence of virus is correlated with the distribution of *Hyalomma* tick species (Principle vector) (4).

Clinical Picture: Sudden onset with initial signs and symptoms including headache, high grade fever, backache, joint pain, upper abdominal pain, vomiting, redness of eyes, a flushed face, sore throat, and petechiae (red spots) on the palate. Symptoms may also include jaundice along with changes in mood and sensory perception. With progression of the illness, 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 hedgehogs, rats, hares and birds are generally resistant with the exception of Ostrich (6).

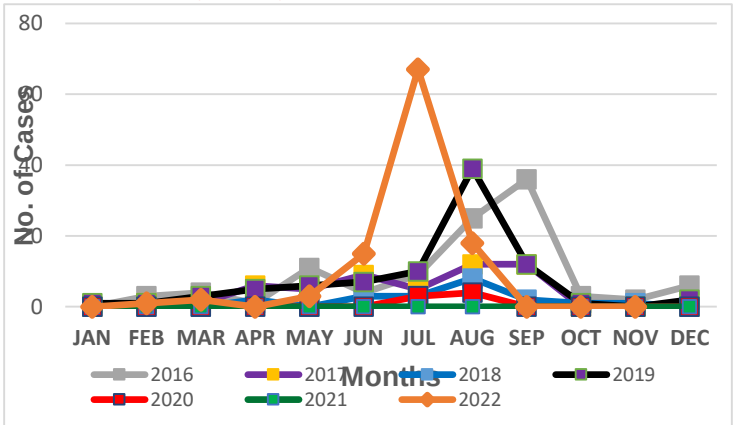
Mode of transmission: Bite of the infected *Hyalomma* tick , handling of tick infested animals, direct contact with blood / tissue of infected domestic animals (slaughtering); or direct contact with blood / tissue of infected patients. Nosocomial infections are common source of transmission (7).

Incubation Period:

- 1-3 days after tick bite
- 5–6 days after exposure to infected blood or tissues with a (documented) maximum of 13 days (8).

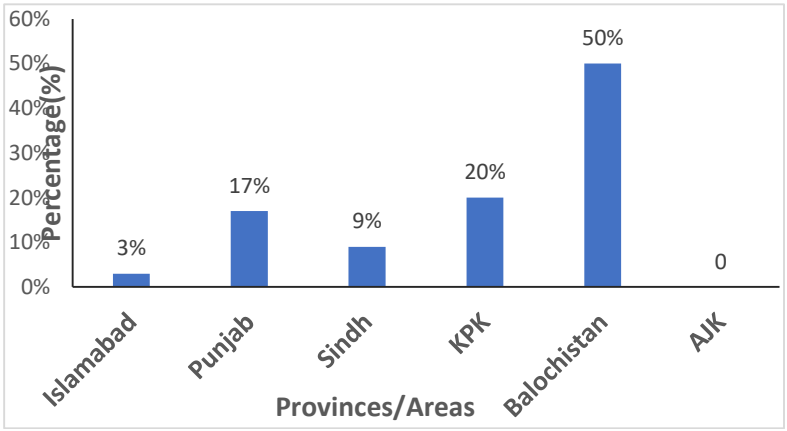
Seasonality: Peak of cases occur during autumn and spring seasons, associated with life-cycle of ticks, exposure of newborn animals, and exposure of migrant animals (9).

Lab Confirmed CCHF Cases by Months from January 2016 to November 2022 (n=375)



Geographical Distribution in Pakistan: Since the diagnosis of first human case of CCHF in 1976, the sporadic cases have been continued to occur all over in Pakistan and predominantly from Balochistan.

Lab Confirmed CCHF Cases by Province/Area from January 2016 to November 2022 (n=375)



Alert Threshold: One probable case is an alert and requires 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 a CCHF endemic area and those in contact with livestock suchas shepherds, butchers, animal handlers and health care personals (11).

Probable Case: Suspected case with history of febrile illness of10 days or less with an epidemiological link AND any two of the following: thrombocytopenia less than 50,000/mm3, petechialor 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 serology (11).

Laboratory Confirmation: Blood for PCR test and ELISA test

Specimen Collection and Transportation: Collect 3-5ml ofblood in vacutainer observing strict biosafety precautions. Keep in upright position to prevent hemolysis. Transport to the laboratory in triple package with ice packs along with a prominent Bio-Hazard label and complete lab request form with brief history of the patient (11).

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) measures i.e. standard plus contactprecautions. Use additional precautions, (droplet/aerosol)in case of any extensive contact/ procedure.
- Only designated medical / para-medical staff and attendants should attend the patient.
- All medical, para-medical staff and attendants should wear recommended Personal Protective Equipment (PPE) before entering the isolation room and must dispose it properly after use.
- All secretions of the patient and hospital clothing in use of the patient and attendants should be treated as infectiousand where possible, should be autoclaved before incinerating.

- Every effort should be made to avoid spills, pricks, injury and accidents during the management of patients. Needlesshould not be re-capped but discarded in proper safety disposal box.
- All used material e.g. syringes, gloves, cannula, tubing etc. should be collected in autoclave-able bags and autoclaved before incinerating.
- After the patient is discharged from the hospital, room surfaces should be wiped down with disinfectant like 0.5% Chlorine concentration, 0.1% Chlorine concentration or 0.05 % Chlorine concentration depending upon the surfaces. The room should be fumigated in case of risk for tick infestation (12).

Treatment: General supportive therapy is the mainstay of CCHF management. 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 attending physician. Studies suggest that Ribavirin is most effective if given within the first 6 days of illness. Oral Ribavirin: 30 mg/kg as loading dose, followed by 16 mg/kg every 6 hours for 4 daysand then 8 mg/kg every 8 hours for net 3 days (12).

Preventive measures: Educate public about the mode of transmission and personal protection. Persons living inendemic areas must be educated on: Avoidance of areas where tick vectors are abundant, especiallywhen they are active (spring to autumn). Regular examinationof clothing and skin for ticks, and their removal (without crushing them). Wearing light colored clothing, covering legsand arms, and using repellents on the skin. Other measures, such as wearing gloves or other protective clothing to preventskin contact with infected tissues or blood, may be taken by persons who work with livestock or other animals. For tick control, animal dipping/spraying in an insecticide solution of Permethrin/Pyrethrin/DEET is used. Injectable insecticide like Ivermectin is also recommended. Butchers should wear glovesand other protective clothing to prevent skin contact with freshly slaughtered meat, blood and other tissues. Meat should be drained for least 30 minutes, before distribution topublic. Hospitals in endemic areas should ensure standard pluscontact precautions in OPD and emergency rooms. Ensure injection safety measures and maintain stockpiling of Ribavirinwith PPE. Bio-safety is the key element to avoid nosocomial infection. Suspected or confirmed CCHF cases must be isolated and cared by using barrier-nursing techniques to prevent transmission of infection to health workers and others. Exposed contacts: Those with high-risk exposure (needle stick, sharps, blood or body fluids) contacts should beobserved for fever for 14 days. If fever develops, Ribavirin should be started immediately (12). There is no approved vaccine available till date (13).

References and Guideline links: *References and guideline available atwww.nih.org.pk and h p://dmc.gov.pk/*

DENGUE FEVER

Introduction: Dengue is a mosquito-borne viral disease (also known as break bone fever), causes flu-like illness, and may develop 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 surge in Dengue cases and the annual epidemic trend in the provinces has been observed multiple times there after [2].

Clinical Picture: Dengue fever: Dengue fever is defined by fever (for >3 days and < 10days) as reported by the patient or healthcare provider andthe 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, thrombocytopenia (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, drowsiness or irritability, pale, cold or clammy skin, difficulty in breathing, a total white blood cells count of <50,000/mm^3 and Platelets count <100,000. **OR**

Dengue shock syndrome (DSS): Defined as a syndrome due to dengue virus 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].

Note: 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: Belonging to *Flavivirus* group; four different Dengue viruses (serotypes) are known: *DEN1, DEN2, DEN3,* and *DEN4* [5].

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

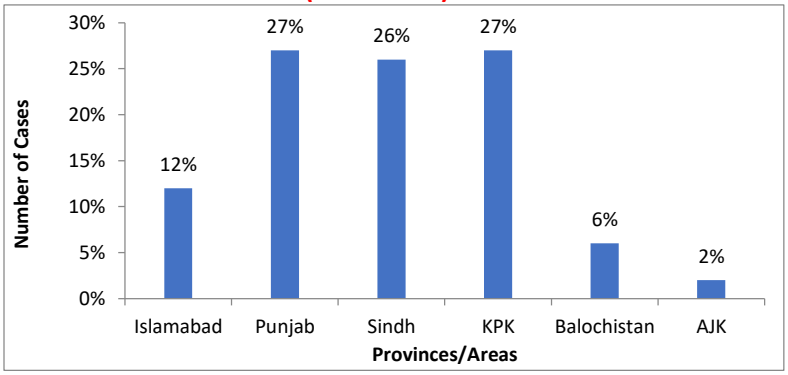
Incubation period: 3-14 days (average 4–7 days) after the infective bite [7].

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

Seasonality: Cases are increased during and after rainy seasonsas compared to winter and summer seasons. Relativelyhumidity, temperature and rain remained significant predictorsof dengue incidence in Pakistan [8] .

Geographical distribution: From January 2015 to June 2021, Sindh & KPK remained the most affected provinces.

Area wise Distribution of Dengue Fever Cases from January 2016 to November 2022 (n=221.903)



Alert threshold for Dengue fever: Cluster of 3 suspected cases

with at least one confirmed case [10].

Alert threshold for Dengue hemorrhagic 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 [11]

Probable Case: A clinically compatible case of Dengue fever, or Dengue hemorrhagic fever with an epidemiologic linkage and 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 in those areas where multiple *flaviviruses* are circulating.

Confirmatory:

- Detection of DENV nucleic acid in serum, plasma, blood by Reverse Transcriptase-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:**

o IgM antibodies are detectable after 4th day of onset of illness (acute).

o 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 mainly 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. Donot give Aspirin or other NSAID like Ibuprofen.
- Extra amounts of fluids Oral rehydration therapy/salt (ORT/ ORS) is recommended for patients with moderate dehydration.
- Complete blood count (CBC/CP) with follow up is an important tool in the management of suspected Dengue patients.
- All Dengue patients must be carefully observed for the signs of shock at least for 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 doesnot need further observation and can be discharged [10].
- **Preventive measures:** Identify mosquito breeding sites, destroy mosquito larval habitats and indoor breeding sites. Community awareness sessions should be conducted in schools, through religious leaders, aiming 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 mosquitoes including use of screening, protective clothing and repellents [10].

Vaccination: First Dengue vaccine, Dengvaxia (CYD-TDV) was registered in several countries for the prevention of the all four Dengue virus serotypes [12]. Moreover, WHO recommends that countries should consider introduction of the CYD-TDV only in geographic settings, where epidemiological data indicate a high burden of disease [13].

References and Guideline links: *References and guideline links are available at online version at www.nih.org.pk and h p://dmc.gov.pk/*

LEISHMANIASIS

Introduction: Leishmaniasis is a parasitic vector borne disease and is classified as a Neglected Tropical Disease (NTD). It can present as cutaneous, mucosal and visceral forms but the most common form is cutaneous Leishmaniasis (1).

Leishmaniasis is one of the prevailing public health issues in Pakistan and is endemic in some areas of Khyber Pakhtunkhwa and Balochistan province from where, disease is continuously reported through DHIS. Since 2011, KP has reported more than 10,000 cases where Karak, Peshawar, Lower Dir and Malakand are the most affected districts. There are more than 6,000 cases reported from merged districts of KP, where most affected tribal district is Bajaur. In Balochistan, DHIS has reported more than 68,000 cases from 2007 to 2018 and more than 2,000 cases were reported in 2019-20.The most affected districts are Quetta, Killa Abdullah, Pishin, Sibi, Jhal Magsi and Khuzdar [2].

Infectious agent: Leishmaniasis is caused by a *protozoa parasite* (3).

Mode of transmission: Spread by the bite of the sand fly on the skin. If animals are the primary host reservoirs, it is called Zoonotic Leishmaniasis, if humans are the primary host reservoirs is called Anthroponotic Leishmaniasis. (Human- sand fly-human) (1).

Incubation period: Considered to be at least a week but may extend up to several months [4].

Case Definition:

1. Visceral Leishmaniasis (VL)

Suspected case: A Person with prolonged irregular fever >2 weeks, weight loss, splenomegaly, hepatomegaly, ascites, diarrhea, cough, anemia and bleeding etc.

Confirmed case: A suspected/ probable case of Visceral Leishmaniasis with serological/parasitological confirmation [5].

2. Cutaneous Leishmaniasis (CL)

Suspected Case: A person presenting with one or more lesions (skin or mucosal), skin lesions typically present on uncovered parts of the body; the face, neck, arms and legs which are the most common sites. The site of inoculation may present with a nodular appearance followed by indolent ulcer [5].

Probable case: A suspected case of VL with serological evidence of infection [5].

Confirmed case: A suspected/probable case confirmed by a positive smear or culture [5].

Diagnostic criteria:

(1) History of residence and travel to Leishmaniasis endemic areas,

(2) Clinically compatible findings,

(3) Laboratory confirmation.

Note: *In endemic malarious areas, visceral Leishmaniasis mustbe suspected when fever is not subsiding or responding to anti-malarial drugs and persists for more than two weeks (assuming drug-resistant malaria has also been considered).*

Specimen Collection:

Cutaneous Leishmaniasis: Skin biopsy is the standard dermatologic technique for obtaining specimen. No preservatives are required for examining LD bodies or for Leishmania culture [5].

Visceral Leishmaniasis: Collect 5ml of clotted blood or serumfor serologic studies. Splenic or bone marrow aspirate collectedin a tube with anticoagulant is required for the demonstration of amastigote. Specimen may be transported at roomtemperature without delay [5].

Laboratory diagnosis: Examination of slides (e.g. of biopsy specimens, impression smears, and dermal scrapings). Serologic testing for detection of antibodies against organisms useful primarily for visceral Leishmaniasis.

Culture: Aspirates of pertinent tissue/fluid (e.g., skin lesion, bone marrow, lymph node, blood/Buffy coat) [6].

Case Management: The treatment of Leishmaniasis depends on several factors including type of disease, concomitant pathologies, parasite species and geographic location. Leishmaniasis is a treatable and curable disease which requiresan immunocompetent system because medicines will not helprid parasites from the body, thus risk of relapse may occurs with immunosuppression of the patient. All patients diagnosed with visceral Leishmaniasis require prompt and complete treatment. Detailed information on treatment of the various forms of the disease by geographic location is available in the WHO technical report series 949,''Control of Leishmaniasis'' [7].

Prevention:

- The majority of the recommended precautionary measures are aimed at reducing the contact with Phlebotominae (sand fly).
- Prevention of ACL is very similar to Malaria, as sand flies biteat night and indoors.
- Permethrin treated bed nets, should be used in endemic areas. Sand flies are generally more sensitive than mosquitoes to insecticide, i.e. residual spraying of indoor rooms for vector control.
- Use of insecticide is unlikely to work in prevention of zoonotic cutaneous, as the sand fly vector tends to bite outdoors, so the most effective strategy is to poison or digup the burrows of reservoir rodents [6].

References: *References links are available at online version at www.nih.org.pk and h p://dmc.gov.pk/*

MALARIA

Introduction: A vector borne parasitic disease transmitted by female Anopheles mosquito species.

With an estimated burden of 1.6 million cases annually, malariais considered as a major public health problem in Pakistan. It contributes 22% of total disease burden in the Eastern Mediterranean Region (EMR). Epidemiologically, Pakistan is classified as a moderate malaria endemic country with national Annual Parasite Index (API) averaging at 1.69 and important diversity within and between the provinces and districts. The two parasites which account for malaria in Pakistan are *Plasmodium Vivax* and *P falcipaum*. The main vectors are *Anopheles Culicifacies* and *Anopheles Stephensi.* This malariogenic potential of Pakistan has a negative impact on country's socio-economic growth and national productivity. (Malaria Control Program Pakistan, 2015-2020)

Clinical Picture: Fever, chills, sweats, headache, nausea and vomiting, body aches and malaise

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 children), and Sweating stage (sweats, return to normal temperature, redness).

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*)

Infectious Agent (s): *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi* (rarely infect humans)

Mode of Transmission: Bite of an infective female Anopheles mosquito and rarely through blood transfusion from infected person.

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

Reservoir: Humans are the only known reservoir.

Infectivity: Humans may infect mosquitoes as long as infective gametocytes are present in the blood. Anopheles mosquitoes remain infective for life.

Seasonality: Malaria in Pakistan is typically unstable and major transmission period is post monsoon i.e. from August to November.

Alert threshold: Number of cases reaches two times the mean number of suspected cases of the previous 3 weeks for a given location.

Outbreak threshold: In endemic area: Slide positivity rate above 50% or falciparum rate above 40%; while in non-endemic area, evidence of indigenous transmission of falciparum.

Case Definitions:

Suspected Case: A case with clinical manifestations of uncomplicated/complicated Malaria.

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

Confirmed Case: Clinical case with laboratory confirmation.

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)

Specimen Collection & Transportation:
Peripheral Blood Film: Collect 3-5ml blood in a tube with anti-coagulant (EDTA).
Case Management: Artemisinin-based combination therapies (ACTs) are there commended 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 isbased on the number of tablets per dose according to reported cases by month in Pakistan, predefined weight bands (5–14 kg: 1 tablet; 15–24kg: 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).

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 anti-malarial dugs (chemoprophylaxis) when appropriate, to prevent infection from developing into clinical disease.
- Immediately seek diagnosis and treatment if a fever develops 1week or more after entering an area where thereis a Malaria risk and up to 3 months (or, rarely, later) afterdeparture from a risk area.

a) Personal protection

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

b) Vector control

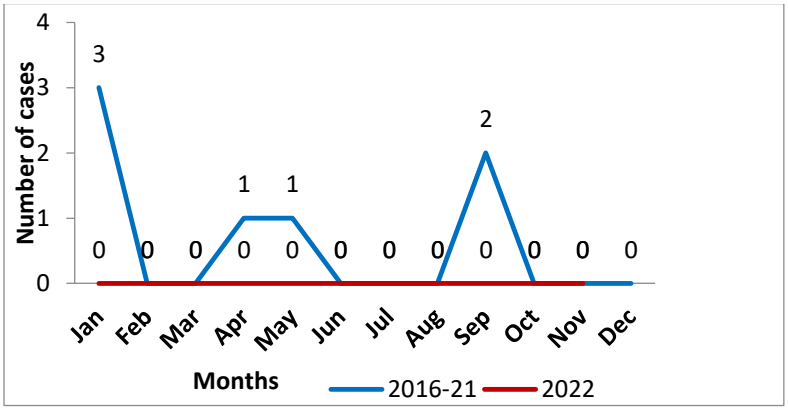
- Indoor spraying with residual insecticides (IRS)Reduce mosquito breeding sites
- Improve vector surveillance
- Optimize the use of resources for vector control through Integrated Vector Management (IVM)

c) Chemoprophylaxis Malaria control Program: Recommended chemoprophylaxis: Atovaquone-proguanil, Doxycycline or Mefloquine
References and Guideline links: *References and guideline links are available at online version at www.nih.org.pk and h p://dmc.gov.pk/*

PERTUSSIS (WHOOPING COUGH)

Introduction: A toxin-mediated disease that can affect people of all ages but can be very serious even deadly among infants. [1]. Despite generally high coverage with childhood vaccines for pertussis, it is one of the leading causes of vaccine-preventable deaths worldwide [2].
Clinical Picture: The clinical course of the illness is divided into three stages: Catarrhal, Paroxysmal and Convalescent. Characterized by uncontrollable, violent coughing which often makes it hard to breathe. The disease usually starts with cold-like symptoms and maybe a mild cough or fever. Coughing fits due to pertussis infection can last for up to 10 weeks or more. Some people know this disease as the "100 days cough". Infants may have a symptom known as "apnea." Pneumonia is the most common complication in all age groups; seizures and encephalopathy generally occur only among young infants [2].
Infectious agent: *Bordetella pertussis*; Gram *negative aerobic bacteria* [3] **Reservoir:** Humans are the only known reservoir [3]
Mode of transmission: By direct contact with discharges from respiratory mucous membranes of infected persons. Airborne/aerosols transmission [3]
Incubation period: 9 -10 days (range 6-20 days) [3]
Communicability: Highly communicable in the early catarrhal stage and gradually decreases after paroxysmal cough. Untreated patients may be contagious for up to 3 weeks after the onset of paroxysmal cough or up to 5 days after onset of treatment [3]
Seasonality: Pertussis has no distinct seasonal pattern [3]

Month wise Lab Confirmed Pertussis Cases in Pakistan from January 2016 to November 2022, (n=07)



Alert Threshold: One suspected case [5]
Outbreak threshold: Five suspected with one lab confirmed case [5]
Case Definition:
Suspected: A person with cough lasting at least 2 weeks withat least one of the symptoms i.e. Paroxysms/ fits of coughing, Inspiratory "whooping", Post-tussive vomiting and apnea in infants with or without cyanosis [6]
Probable case: A clinical suspected case with an epidemiological linkage [5]
Confirmed case: Suspected/Probable case confirmed with positive laboratory result [5]
Lab confirmation: Culture is the gold standard. Detection of genomic sequences by polymerase chain reaction (PCR). positive paired serology [5]

Specimen Collection:

- Collect two nasopharyngeal specimen using calcium alginate swabs on fine flexible wire.
- Bronchial or nasopharyngeal secretions/aspirates may provide superior specimens for culture.
- Collect throat swabs in addition to the nasopharyngeal swabs for isolation of organism on culture.

Storage: Can be stored at room temperature for 48 hours, refrigerated for 7 days and frozen for 30 days [5] **Packaging:** Triple packaging seal in a biohazard bag [5] **Transportation:** Reagan Lowe (RL) transport medium [5] **Case Management:** Antibiotic treatment should be initiated inall suspected cases.

Treatment options include:

Erythromycin 500mg, 6 hourly for 7 days. Clarithromycin 500mg orally twice daily for 7 days. Other macrolides as prescribed by the physician. Young infants particularly those younger than 6 months of age should be hospitalized immediately. Supportive case management including cough suppressant and good nursing care. Maintenance of proper water and electrolyte balance, adequate nutrition and sufficient oxygenation [6].

Preventive measures & vaccination:

- Timely treatment of the cases decreases the risk of transmission
- Immunization: Active primary immunization against *B. pertussis* infection with the whole-cell vaccine (WP) is recommended. Children who have received at least 3 doses are estimated to be protected especially against severe disease. However, protection begins to wane after about 3 years [5].

Vaccination during pregnancies: It is important for women toget the whooping cough vaccine during 27th week through 36thweek of pregnancy [5]. Return to school: Infected child should avoid school / day care until they have completed 5 days course of therapy or if not treated 21 days after the onset of symptoms[5].

References:

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

POLIOMYELITIS

Introduction: A potentially disabling and life threatening viral infectious disease that can affect nerves and can lead to partialor full paralysis among a proportion of infected children;mainly under 5 years of age. Once affected, the paralysis hasno cure, but it can be easily prevented through safe and effective vaccines administered orally (OPV) as well as throughinjections (IPV).

The disease is marked for global eradication through the World Health Assembly resolution in 1988.The efforts so far reduced endemic countries from 125 to only 2 including Pakistan, and Afghanistan.

Polio was declared as a Public Health Emergency ofInternational Concern (PHEIC) by WHO on 5th May, 2014 andcontinues to stay as such till date. Pakistan is classified by theInternational Health Regulations (IHR-2005) as a state beinginfected with WPV1, cVDPV1 or cVDPV3 with potential risk ofinternational spread. Therefore the Government of Pakistanhas also declared Polio as a national public health emergencyand an annually updated National Emergency Action Plan(NEAP) is being implemented nationwide under the overallsupervision of the National Task Force led by the PrimeMinister of Pakistan and taking on board all provincial chiefministers as well as Prime Minister of AJK.

Geographical Distribution in Pakistan:

Clinical Picture: There are three basic phases of Polio virus infection: subclinical, non-paralytic, and paralytic. Mostly infection remains asymptomatic but Poliovirus may cause Acute Flaccid Paralysis (AFP); one in 200 infections. The onset of asymmetric paralysis is usually sudden coupled with fever. The severity of weakness also varies with the level of immunity among the affected child rendered through immunization. Weakness is ascending and may vary from one muscles or group of muscles, to quadriplegia, and respiratory failure. Proximal muscles usually are affected more than distal muscles and lower limbs more than the upper limbs. Reflexes are decreased or absent while sensory examination may be normal (6).

Lab. Confirmed Polio Cases By Province/Area In Pakistan

Province/Area	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Islamabad	0	0	0	0	0	0	0	0	0	0	0
Punjab	2	7	5	2	0	1	0	12	14	0	0
Sindh	4	10	30	12	8	2	1	30	22	0	0
Khyber Pakhtunkhwa	27	11	68	17	8	1	2	93	22	0	20
KPTDS	20	65	179	16	2	0	6				
Balochistan	4	0	25	7	2	3	3	12	26	1	0
GB	1	0	0	0	0	1	0	0	0	0	0
AJK	0	0	0	0	0	0	0	0	0	0	0
Total	**58**	**93**	**307**	**54**	**20**	**8**	**12**	**147**	**84**	**1**	**20**

Infectious agent: Poliovirus belongs to genus *Enterovirus* subgroup, family *Picornaviridae*, having three serotypes of Poliovirus, labelled P1, P2, and P3 (7).

Reservoir: Humans are the only known reservoir (7).

Mode of transmission: Primarily person to person spread through the fecal-oral route. After initial infection with the poliovirus, the virus is shed intermittently in faeces for several weeks

Note: After initial infection with Poliovirus, the virus is shed intermittently in faeces for several weeks

Incubation Period: 7 -14 days for paralytic cases (range 3 - 35 days) (7)

Alert & outbreak threshold: One suspected case of polio is an alert/outbreak and requires an immediate notification and stools sample collection for confirmation (8)

Case Definition: This sensitive case definition will capture Poliomyelitis but also other diseases, including Guillain-Barre syndrome (GBS), Transverse Myelitis and Traumatic Neuritis, such that each case with limping must be investigated carefully (9).

Suspected Case: Recent/ Sudden onset of floppy/flaccid weakness in a child below 15 years of age due to any cause including GBS **OR** any illness in a person of any age if clinically polio is suspected by a medical doctor (9).

Polio-compatible AFP: A case in which one adequate stool specimen was not collected from a probable case within 2

weeks of the onset of paralysis, and there is either an acute paralytic illness with polio-compatible residual paralysis at 60 days, or death takes place within 60 days, or the case is lost to follow-up (9).

Vaccine-associated Paralytic Poliomyelitis case: A case with acute paralytic illness in which vaccine-like poliovirus is isolated from stool samples, and the vaccine derived virus is believed tobe the cause of the paralysis (9).

Confirmed Polio case: A case with acute paralytic illness, withor without residual paralysis, and isolation of wild poliovirus from the stools of either the case or its contacts (9).

Discarded case: A case with acute paralytic illness for which one adequate stool specimen was obtained within 2 weeks after onset of paralysis and was negative for poliovirus (9).

Specimen Collection & Transportation: Collect two 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. (10).

Public Health Measures: Four pillars of polio eradication as public health measures include:

1. Achieving a high level of coverage with at least 4 doses of the oral poliovirus vaccine (OPV) and one dose of IPV in routine.
2. Providing supplementary doses of OPV to all children <5 years old during NIDs and SNIDs, as well as the caseresponse planned by the Polio Eradication Program.
3. Active and Passive Surveillance for all cases of acute flaccid paralysis
4. House-to-house OPV campaigns, targeting areas in which transmission of wild Poliovirus persists, based on National Emergency Action Plan (NEAP 2019-2020) (11).

Current Situation: There had been no confirmed Polio case since one and a half year but recently 08 confirmed Polio cases have been reported from North Waziristan.

References links: *References links are available at online version at www.nih.org.pk and h p://dmc.gov.pk/*

PROBABALE DIPHTHERIA

Introduction: An acute, toxin-mediated vaccine preventable upper respiratory tract illness that affects the throat and sometimes tonsils. Diphtheria causes a thick covering in the back of the throat and can involve any mucous membrane. Classification based on sites of disease are anterior nasal, pharyngeal & tonsillar, laryngeal, cutaneous, ocular and genital [1].

Clinical Picture: Sore throat, low grade fever and an adherent pseudo-membrane on the tonsils, pharynx and/or nasal cavity. Symptoms range from sore throat to toxic life-threatening diphtheria of the larynx or of the lower and upper respiratory tracts. The toxin produced by bacteria may also get into the blood stream and can cause damage to the heart, kidneys, and nerves [1].

Infectious Agent: *Corynebacterium diphtheriae*, an aerobic toxin producing gram positive bacillus. *C. diphtheriae* has 4 biotypes i.e. gravis, intermedius, mitis and belfant [1].

Reservoir: Humans are the reservoir for *C. diphtheriae* and are usually asymptomatic [2]

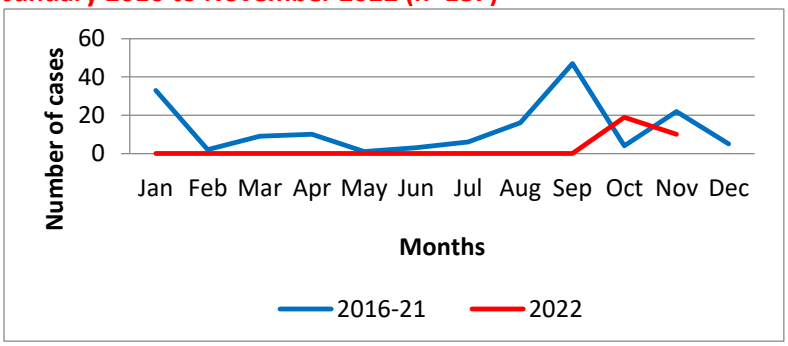
Mode of Transmission: Transmitted from person to person, usually through respiratory droplets (coughing or sneezing).Infection may come by contact/touching open sore (skin lesions) and material objects (cloths, fomites) used by the patient of Diphtheria. Raw milk may also serve as a vehicle [2].

Incubation Period: Usually 2-5 days, occasionally longer [2].

Infectivity/Communicability: Organisms usually persist 2 weeks or less and seldom more than 4 weeks. Chronic carriers may shed infectious agent for 6 months or more [2].

Seasonality: Throughout the year; higher incidence is in winter and spring [3].

Month Wise Lab Confirmed Diphtheria Cases in Pakistan from January 2016 to November 2022 (n=187)



Alert Threshold: One probable case is an alert [3] **Outbreak Threshold:** One lab confirmed case is an outbreak [3]**Case Definition**:

Probable Case: In the absence of a more likely diagnosis, an upper respiratory tract illness with each of the following:

- An adherent membrane of the nose, pharynx, tonsils, or larynx;
- Absence of lab confirmation; AND
- Lack of epidemiological linkage to a lab confirmed case of Diphtheria [4].

Confirmed Case: Any probable case that has been laboratory confirmed or linked epidemiologically to a laboratory confirmed case [4].

Carrier: A person with no symptoms but has laboratory confirmation of a toxigenic strain

Discarded: Any probable case in whom other compatible organisms are isolated or if *C. diphtheriae/ C. ulcerans/ C. pseudotuberculosis* is isolated but is confirmed to be a non-toxigenic strain [3]

Lab Confirmation:

- Conventional culture method (bacteriological culture testing)

Specimen Collection and Transportation:

- Collect nasopharyngeal and throat swabs by using polyester, or nylon swabs.
- Pieces of pseudo-membrane may also be submitted in sterile saline [not formalin] for culture.
- The swabs should be placed in transport media such as

Amies or Stuart respectively at ambient temperature [3].

Timings: Specimens for culture should be obtained as soon as diphtheria [involving any site] is suspected, even if treatment with antibiotics has already begun [1].

Case Management:

For Patients:

- Do not wait for laboratory results before starting treatment/ control activities. All cases must receive diphtheria antitoxin (DAT)
  - For mild pharyngeal or laryngeal disease, the dose: 20,000 – 40,000 units
  - For moderate nasopharyngeal disease, the dose: 40,000 - 60,000 units
  - For severe, extensive or late [3 or more days] the dose: 80,000 – 100,000 units
- Removal of membrane by direct laryngoscopy or bronchoscopy may be necessary to prevent or improve airway obstruction.
- Either penicillin 250 mg orally 6 hourly daily or erythromycin 500 mg orally 6 hourly is effective therapy, although erythromycin is slightly more effective in eliminating the carrier stage, should be continued for 14 days.
- Other microlides are probably as effective as erythromycin.
- The patient should be isolated until three consecutive cultures at the completion of therapy have documented elimination of the organism from oropharynx.

Preventive measures:

- Standard plus droplet precautions are recommended with single room isolation.
- Primary prevention of disease by ensuring high population immunity through immunization.
- Secondary prevention of spread by the rapid investigation of close contacts to ensure their proper treatment.
- Tertiary prevention of complications and deaths by early diagnosis and proper management [1].

Vaccination:

- Routine immunization consists of 3 doses of 0.5 ml DPT-Hep-B-Hib (Pentavalent Vaccine) administered IM to all thechildren less than one year of age with the schedule of:
  a. 1stdose at the age of 6 weeks;
  b. 2nd at 10 weeks;
  c. 3rd at 14 weeks, a booster DTP at 18 months to 4 years.
- If children or adults have not been immunized with three-dose series, children < 5 years should receive DT vaccine, and children ≥ 5 years and adults should receive Td vaccine to complete a series of three doses [1]

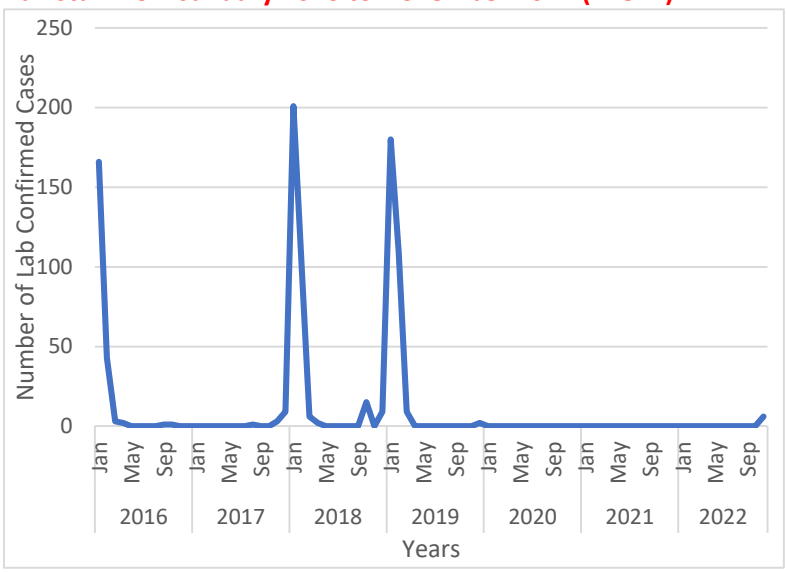
References:

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

SEASONAL INFLUENZA

Influenza is a contagious respiratory illness caused by *influenza virus.* It can cause mild to severe illness. Older people, young children and people with co morbidities are at high risk for having serious complications. There are 4 types of seasonal influenza viruses, types A, B,C and D. Influenza type A viruses are further classified into subtypes and currently circulating among humans are influenza-A(H1N1) and A(H3N2) subtypes. In Pakistan, the influenza activity typically starts increasing from September and reaches peak during the winter months. Clinicians to remain vigilant and treat all suspected cases of severe influenza appropriately [3].

Month wise Lab Confirmed Seasonal Influenza H1N1 Cases in Pakistan from January 2016 to November 2022 (n=871)



Clinical Picture: Seasonal influenza is characterized by a sudden onset of fever, cough (usually dry), headache, muscle and joint pain, severe malaise (feeling unwell), sore throat and a runny nose. The cough can be severe and can last two weeks or more. Most people recover from fever and other mild symptoms within a week without seeking medical attention. But influenza can cause severe illness or death especially in high risk groups [4].

Case definitions for influenza surveillance: As of January 2014, the WHO global influenza surveillance standards define the surveillance case definitions for influenza-like illness (ILI) and severe acute respiratory infections (SARI) [5]

Influenza Like illness (ILI): An acute respiratory infection with measured fever of ≥ 38°C with cough **AND** onset within the last 10 days [5].

Severe Acute Respiratory Illness (SARI): An acute respiratory infection with history of fever or measured fever of ≥ 38°C and cough with onset within the last 10 days **AND** requires hospitalization [5].

Sample Collection & Transportation: Respiratory specimens including throat or nasopharyngeal swabs and nasopharyngeal aspirates/ Broncho-alveolar lavage fluid from intubated patients may be collected and placed immediately in Viral Transport Medium (VTM). The samples may be transported to lab at 4 °C within 4 days, or frozen at -70 °C in case of prolonged storage.

Management: The symptoms in mild illness are relieved by providing warm fluids and taking rest along with analgesics and antipyretics. Analgesics such as Paracetamol 500mg-1G every4-6 hours usually relieves headache and generalized pains and cough suppressants such as pholcodine 5-10 mg, 3-4 times daily are generally sufficient. Antimicrobial agents are not effective against viruses, treatment with antibiotics for superadded bacterial infection such as bronchitis and

pneumonia may be necessary [7].

Note: *Patients not considered being at higher risk of developing severe or complicated illness and who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals* [7].

Difference between Flu and COVID-19;

- Influenza (Flu) and COVID-19 are both contagious respiratory illnesses, however COVID-19 is caused by infection with a new coronavirus (called SARS-CoV-2), andflu is caused by infection with influenza viruses.
- COVID-19 seems to spread more easily than flu and causes more serious illnesses in some people. Incubation period of COVID-19 is 2 to 14 days, while flu has incubation period of 1to 4 days.
- Because some of the symptoms and modes of transmissionof flu and COVID-19 are similar, it may be hard to tell the difference between them based on symptoms alone, thus COVID-19 specific lab testing, may be required to help confirm a differential diagnosis.

Prevention and Public Health Measures: Annual winter vaccination (seasonal anti-influenza vaccine) is recommendedfor health care workers, pregnant women, young children and immuno-compromised patients specially patients with pulmonary, cardiac or renal diseases. About two weeks after vaccination, antibodies develop that protect against influenza virus infection. General precautions include improved ventilation in living places; avoiding close contact with ill people and crowded settings, avoiding touching mouth and nose and regular hand washing with soap. Patients should be encouraged to cover their faces with a mask or handkerchief when coughing and sneezing [8].

Advisory link: https://www.nih.org.pk/wp-content/uploads/2019/10/Advisory-for-the-Prevention-and-Control-of-Seasonal-Influenza.pdf

References:

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

TYPHOID FEVER

SALMONELLA ENTERICA SEROVAR TYPHI
(Extensively drug resistant strain)

Introduction: A life-threatening illness that affects more than21 million people in the developing world. Multidrug-resistant(MDR) isolates are prevalent in different 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 Cephalosporinor Azithromycin have also been reported.

Since 2016, the first large-scale emergence and spread of a novel *S. typhi* clone harbouring 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).

Infectious agent: Anti-microbial resistant (AMR) strains of *Salmonella enterica serovar typhi* **Clinical picture:** Patient presents with high grade fever (>38°C), weakness, abdominal pain, headache and loss of appetite. In some cases, patients have a rash of rose-colored spots.

Mode of Transmission: Typhoid infection occurs through feco-oral route and infection spreads through contaminated food, milk, frozen fruits and water or through close contact with already infected persons.

Incubation period: Depends on the inoculum size and host factors; 3 days to more than 60 days with a usual range of 8 to 14 days.

High risk groups: Preschool children are at greater risk of developing disease and usually have milder symptoms than the adults do. Travelers to, or workers in endemic areas and care givers of the patient infected with *S. Typhi* are also at higher risk.

Reported XDR Typhoid Fever Cases in Sindh by Years (November 2016 to August 2021)

Years	Karachi	Hyderabad	Other Districts	Sindh Total
2016	0	12	0	12
2017	175	485	4	664
2018	3712	891	207	4810
2019	7088	1645	998	9731
2020	2510	708	415	3633
2021	1739	360	175	2274
Total	15224	4101	1799	21124

(Source: FDSRU-NIH weekly Report Volume 3-- Issue 33, August 08-14 , 2021Date: August 18, 2021

Suspected Case: Any person with history of fever of at-least 38°C for 3 or more days with abdominal symptoms like weakness, diarrhea, constipation, and abdominal tenderness.

Confirmed Case: A suspected/ probable case that is laboratory confirmed by isolation of *S. Typhi* from blood/ stool or urine.

Classification of Typhoid Fever Case Definitions by Drug Resistance Status, Pakistan (WHO-2018-2020)

Classification	Case Definition
Non-resistant Typhoid Fever	Typhoid fever caused by *Salmonella Typhi* and/or Salmonella Paratyphi A,B or C strains which are sensitive to first line- drugs and third generation cephalosporin, with or without resistance to second-line drugs
Multi-drug resistance (MDR) Typhoid fever	Typhoid fever caused by *Salmonella Typhi* and/or Salmonella Paratyphi A,B or C strains which are resistant to the first-line recommended drugs for treatment, with or without resistance to second-line drugs
Extensive Drug Resistant (XDR) Typhoid fever	Typhoid fever caused *by Salmonella Typhi* strain which are resistant to all the recommended antibiotics to the typhoid fever

(Source: FDSRU-NIH weekly Report Volume 3-- Issue 22,May 23-29 , 2021 Date: June 02, 2021

Lab Diagnosis:

The only way to confirm Typhoid fever is blood culture, bone marrow culture, or stool sample tested for the presence of *S. Typhi*.

S. Typhi can be isolated from blood during the first week ofillness or from stool and urine after the first week of illness.

Widal and Typhoid have *NO diagnostic value* due to limited sensitivity, specificity and cross reactivity and must be stopped immediately by all labs.

The XDR Typhoid cases information and lab culture report must be notified to the concerned district health authorities, DG Offices of the respective provinces and the NIH.

Treatment: Suspected cases having history compatible with the case definition(s) should immediately seek medical advicefrom health care facilities.

COVID-19 Situation and Antibiotics Prescribing Practices in Pakistan: Since the emergence of COVID-19, it has been observed that health care professionals are frequently prescribing azithromycin for the treatment of suspected and confirmed COVID-19 infections. The increased use of azithromycin for the COVID-19 patients may develop resistance strains against the azithromycin, and consequently their spread which will further limit out the treatment options in the XDR Typhoid cases. This practice should therefore immediately be addressed and azithromycin must carefully be prescribed for COVID-19 cases based on national and international recommendations**.**

Preventive measures and Vaccination: It is suggested that with the treatment options for typhoid becoming more limited, following preventive measures are urgently needed, including improved sanitation and vaccination campaigns:

- Use of azithromycin and meropenem should be restricted and only given to XDR cases of Typhoid fever based on prescription by registered medical practitioner.
- In case of other infections such as upper and lower respiratory tract infections, other available drug options should be used instead of oral azithromycin which should be spared/ reserved for lab confirmed XDR Typhoid cases andother serious medical conditions.
- Raising community awareness on the following:
- Thorough hand washing with soap and water is highly recommended after using toilet, before and after attending patient, before handling, cooking and eating.
- Drink treated, boiled or bottled water. Use ice, prepared from clean drinking water preferably boiled. Wash fruits and vegetable properly before eating. Eat freshly cooked,hot served and home-made food.
- Avoid eating raw fruits or vegetables, market prepared or leftover food.
- Use pasteurized milk.
- Vaccination should be considered especially for those who are travelling to and from endemic areas, high risk group of people and those who are exposed to the disease. Typhoidfever vaccines do not provide 100% protection; however, they will reduce the severity of the illness.
- Typhoid conjugate vaccine (Typbar-TCV@) is a new conjugate vaccine with longer immunity. WHO has prequalified the first conjugate vaccine in December 2017to prevent Typhoid fever

References and Guideline links: *References and guideline links are available at online version at www.nih.org.pk and h p://dmc.gov.pk*

Potential National Public Health Events

Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS):

The human immunodeficiency virus (HIV) infects cells (CD4 cell a type of T cell) of the immune system, destroying or impairing their function. Infection with the virus results in progressive deterioration of the immune system, leading to "immune deficiency." The immune system is considered deficient when it can no longer fulfill its role of fighting infection and disease. Infections associated with severe immunodeficiency are known as "opportunistic infections", because they take advantage of a weakened immune system. Acquired immunodeficiency syndrome (AIDS) is a term which applies to the most advanced stages of HIV infection and is often characterized by the presence of any of the more than 20 associated opportunistic infections, complications or cancers.

Present situation in Pakistan: HIV is endemic in many parts of the country. According to Pakistan National AIDS Control Program data December 2020, there are 0.18 million estimated people with HIV, 42,563 registered people living with HIV who know their status in 45 Antiretroviral Therapy (ART) centers and 24,606 people are currently receiving ARV therapy.

Preventive measures and control: Promote Injection safety practices which includes, safe phlebotomy practices, safe disposal of sharps and healthcare waste. Reduce sexual transmission of HIV including uptake of appropriate HIV preventive measures including safe sex practices and promotion of the use of condoms. Modify the risk behavior of people in the community through “behavior change communication” (BCC). Sexually transmitted infections (STIs) control practices especially for sex workers, usingthe syndromic STIs management approach with partner notification and promotion of safer sex. Preventing the transmission ofHIV through infected pregnant women to infants by the use of antiretroviral therapy (ART) i.e. Teneforvir, Emtricitabine and Raltegravir throughout pregnancy.

Occupational exposure: If a person has had occupational exposure to HIV, the following regimen is preferred; Emtricibine plus Tenofovir along with Raltegravir or Dolutegravir for a duration of 4 weeks depending on the type of exposure.

Guideline links:

Guideline links: https://www.nih.org.pk/wp-content/uploads/2019/05/Advisory-for-the-Prevention-and-Control-of-HIVAIDS.pdf

Potential International Public Health Event

Monkeypox Disease (Mpox)

Monkeypox is a viral zoonotic disease very first observed among monkeys kept for research in 1958 in Copenhagen, later on the disease was observed first in 9 months old child form Democratic Republic of Congo in 1970. Since then, the disease is endemic in Central and West African countries. Monkeypox virus is part of the same family of viruses as variola virus, the virus that causes smallpox. Monkeypox symptoms are similar to smallpox symptoms, but milder, and monkeypox is rarely fatal. Monkeypox is not related to chickenpox. In 2003, the first monkeypox outbreak outside of Africa was in the United States of America and was linked to contact with infected pet prairie dogs. These pets had been housed with Gambian pouched rats and dormice that had been imported into the country from Ghana. This outbreak led to over 70 cases of monkeypox in the U.S. In May 2022, multiple cases of monkeypox were identified in several non-endemic countries. Currently, the disease is being reported from more than 108 countries mostly from US, followed by Spain, Brazil, France and UK. it is less severe with case-fatality less than 1%. World Health Organization declared Monkeypox as Public Health Emergency of International Concern (PHEIC) on 25th June 2022.

Transmission: Human-to-human transmission can result from close contact with respiratory secretions, skin lesions of an infected person or recently contaminated objects. Transmission via droplet respiratory particles usually requires prolonged face-to-face contact, which puts health workers, household members and other close contacts of active cases at greater risk. The disease is observed to be more common among immune-compromised people, men sex with men (MSM)

Clinical presentation: Monkeypox typically presents with fever, itching, rash and generalized lymphadenopathy. The presentation of rash is different from Small pox and chickenpox. It starts to appear 2-3 days after the onset of fever in the form of macules, later with interval of 2-3 days it changes into papules, vesicles and pustules. After 21-24 days, it can heal spontaneously leaving a depressed scar.

Laboratory confirmation: swabs taken from vesicular fluid or lesion crust can be processed for Real-time PCR confirmation which is more reliable to diagnose the virus.

Clinical Management: Clinical care for monkeypox should be fully optimized to alleviate symptoms, manage complications and prevent long-term sequelae. Patients should be offered fluids and food to maintain adequate nutritional status. Secondary bacterial infections should be treated as indicated.

Preventive Measures: Raising awareness of risk factors and educating people about the measures they can take to reduce exposure to the virus is the main prevention strategy for monkeypox. Scientific studies are now underway to assess the feasibility and appropriateness of vaccination for the prevention and control of monkeypox. Some countries have, or are developing, policies to offer vaccine to persons who may be at risk such as laboratory personnel, rapid response teams and health workers.

Vaccination: Vaccination against smallpox was demonstrated through several observational studies to be about 85% effective in preventing monkeypox. Thus, prior smallpox vaccination may result in milder illness. Some laboratory personnel or health workers may have received a more recent smallpox vaccine to protect them in the event of exposure to orthopoxviruses in the workplace. A still newer vaccine based on a modified attenuated vaccinia virus (Ankara strain) was approved for the prevention of monkeypox in 2019. This is a two-dose vaccine for which availability remains limited. Smallpox and monkeypox vaccines are developed in formulations based on the vaccinia virus due to cross-protection afforded for the immune response to orthopoxviruses.

Guidelines link: https://www.nih.org.pk/wp-content/uploads/2022/05/Alert-Multi-Country-Monkey-Pox-outbreak-in-Non-endemic-Countries.pdf

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National Institute of Health, Islamabad

This document can also be accessed at NIH Website www.nih.org.pk , Email: eic.nih@gmail.com
Ph: +92-51-9255237, Fax: +92-51-9255575