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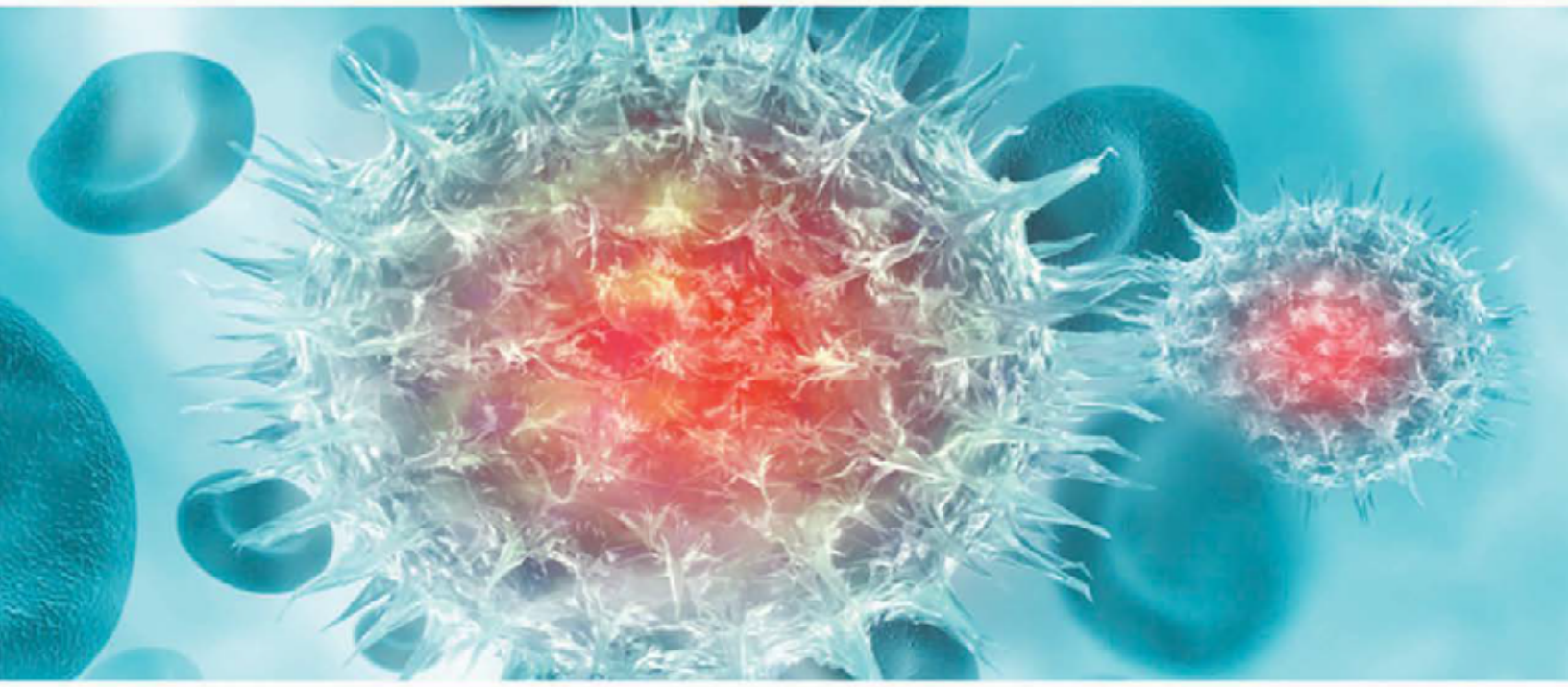

Comprehensive Textbook of INFECTIOUS DISEASES

MI Sahadulla | Sayenna A Uduman

SECOND EDITION

JAYPEE

Comprehensive Textbook of
Infectious Diseases

Second Edition

Editors-in-Chief

MI Sahadulla
MD FRCP (Ire) FRCP (Lon) MBA
Chairman and Managing Director
Kerala Institute of
Medical Sciences (KIMS)
Health Care Group
Thiruvananthapuram, Kerala, India

Sayenna A Uduman
MD FAAP
Visiting Professor and
Clinical Associate
Member, HIC Committee
Kerala Institute of Medical Sciences (KIMS)
Thiruvananthapuram, Kerala, India
Professor Emeritus of Pediatrics and Pediatric Infectious
Diseases and Clinical Virologists
Emeritus Fellow American Academy of Pediatrics

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Contents

1. **Infectious Disease Subspecialty Role in Indian Healthcare Settings** 1

2. **Antibiotic Strategies in the Era of Multidrug Resistance** (From Penicillin to Polymyxins-E and Beyond) 4
   - Historical: Therapeutic Gains and Resistance of Antibiotics *4*
   - Causes of Antimicrobial Drug Resistance *6*
   - Approaches to Control the Resistance Spread *9*
   - Rapid Pathogen Identification (Nonculturing) and Bacterial Resistance Determinant Detection *12*
   - Pathogen-Specific Antibiotic Drugs *14*
   - Fundamentals of Traditional and Evolving Antibiotics (Therapeutic Antimicrobial-Armamentarium in Clinical Medicine) *23*
   - Newer Drugs and New Uses for Older Drugs *32*
   - Antibiotics against Bacterial Enzymes: [β-lactamase Enzymes and β-lactamase Inhibitors (β-lactamase Inhibitors with β-lactam Core Antibiotics)] *37*
   - Next Frontier for Treatment of MDR, XDR, and PDR Pathogens *38*
   - Consequences of Antimicrobial Resistance *39*
   - Antibiotic Stewardship Program *39*
   - Antimicrobial Formulary Restriction Status *42*
   - Tuberculosis Medications and Drug-Resistance TB *42*
   - Approach to the Patient with a History of Penicillin Allergy *46*
   - Probiotics as a Treatment for Infectious Diseases *48*

3. **Febrile Illnesses and Pictorial Skin Rashes** (Acute Onset Fever with No Focus of Infections) 50
   - Fever of Unknown Origins *50*
   - Fever Illnesses with Skin Rashes (Etiologic Agents Causing Febrile-Rash Illnesses) *52*
   - Monthly Trends (2016–18) for Selected Notified Febrile IDs with and without Rashes Seen for the Entire Kerala State and at KIMS Hospital, Thiruvananthapuram *57*

4. **Lingering Fever beyond Malaria in Indian Healthcare Settings** 61
   - Enteric Fever (Typhoid and Paratyphoid) *61*
   - Nontyphoidal Salmonella *63*
   - Scrub Typhus (Mite-Borne) and Bush Typhus Fever *64*
   - Leptospirosis *66*
   - Human Brucellosis *68*

5. **Mosquito-borne Malarial and Viral Diseases** 70
   - Background: Mosquitoes Involved in Human Diseases *70*
   - Malarial Protozoal Infection *70*
   - Mosquito-borne Viral Diseases: Dengue, Chikungunya and Zika Viruses *75*
   - Zika Virus: Virus Pathway—Historical/Clinical/Laboratory Testing Aspects *81*
   - Mosquito-borne Neuroinvasive Viral Diseases: (Japanese Encephalitis Virus, Yellow Fever Virus/West Nile Virus, St Louis Encephalitis Virus and La Crosse Virus) *86*
   - Mosquito Bite Protection Aspects *90*

JAYPEE BROTHERS

6. Tick-borne Diseases (Bacterial and Viral Causes) 91
- Tick-borne Bacterial Infections *91*
- Tick-borne Viral Infections *95*

7. Viral Hemorrhagic Fevers 97
- Viral Hemorrhagic Fevers *97*
- Crimean-Congo Hemorrhagic Fever *97*
- Hantavirus *98*
- Marburg and Ebola (Filoviruses) *98*
- Kyasanur Forest Disease Fever *101*
- Lassa Fever *101*

8. Central Nervous System (CNS): Acute Infections 102
- Background of Acute CNS Infections *102*
- Meningitis *102*
- Sepsis and Septic Shock *105*
- Brain Abscess (Focal CNS Infections) *107*
- CNS Shunt Infection *110*
- Poliomyelitis and Non-Polio Acute Flaccid Paralysis and Acute Flaccid Myelitis Syndromes *110*
- Chronic Meningitis (Subacute or Chronic Leptomeningitis with or without Encephalitis) *111*
- Aantimicrobial Doses for CNS Infections (Adults/Newborn/Pediatrics) *113*

9. Encephalitis: Infectious and Immune-mediated (Infectious, Parainfectious Immune-mediated and Noninfectious Encephalitis Disorder) 115
- Infectious or Primary Encephalitis (Acute Viral Encephalitis) *115*
- Nipah Virus-associated Encephalitis *118*
- Human Herpesvirus 6 (Including Roseola Infantum) and 7 *119*
- Human Parechovirus Encephalitis *119*
- Postinfectious or Secondary Encephalitis *120*
- Syndromes of Antibody-mediated Autoimmune Encephalitis *120*
- Acute Disseminated Encephalomyelitis Syndrome *122*
- Guillain–Barrè Syndrome *124*
- Rasmussen's Focal Encephalitis *125*
- Bickerstaff's Brainstem Encephalitis *125*
- Subacute Sclerosing Panencephalitis *126*
- Prion Diseases of the Central Nervous System *126*

10. Skin and Soft Tissue Infections in Adults/Children 129
- Erysipelas and Cellulitis *129*
- *Staphylococcus aureus* Overview *132*
- Community-acquired MRSA *132*
- Management of Recurrent MRSA Skin Infections *133*
- Necrotizing Fasciitis (Serious and Deep-Tissue Infections) *133*
- Toxic Shock Syndrome: *Staphylococcus aureus* versus GAS Causing *134*
- Diabetic Foot Infections *136*
- Surgical-Site Infections *137*

11. Pricks, Bites and Scratches (Precaution and Preventions) 139
- Needle Stick Injuries (Pricks) *139*
- Animal Bites including Reptiles (Snake) *142*

JAYPEE BROTHERS

- Rabies *143*
- Rodent-borne (Rat Borne) Diseases *144*
- Human Bites and Clenched-fist Injuries *145*

12. Infectious Diseases of the Head and Neck 147
- Head and Neck Infections *147*
- Acute Streptococcal Pharyngitis ("Strep Throat") *149*
- Acute Otitis Media and Mastoiditis *154*
- Acute Epiglottitis *158*
- Orbital and Periorbital Cellulitis *158*

13. Pulmonary Infections: Adults and Childhood.....160
- Background of Respiratory Infections *160*
- Adult (CAP) Pneumonia in Hospitalized Patients *161*
- Healthcare-acquired Pneumonia *164*
- Ventilator-associated Pneumonia *165*
- Legionnaires' Disease *166*
- COPD Exacerbations *167*
- Special Consideration: Immunodeficiency, Cystic Fibrosis and Sickle Cell Disease *168*
- Pertussis in all Age Groups *168*
- Pediatric Pneumonia *169*

14. Tuberculosis and NTM Infections Including *M. leprae* (Adults and Childhood) 177

TB and NTM 177
- Tuberculosis Key Messages *177*
- Natural History: Tuberculosis Disease and Infection *178*
- Tuberculosis Latency (Latent Tuberculosis Infection) *178*
- Clinical and Diagnostic Key Points *180*
- Drug Resistance and Role of Rapid GenExpert Assay *181*
- Antituberculosis Drugs *182*
- Pediatric Tuberculosis and BCG Prevention Role *183*
- Nontuberculous Mycobacterial Infections *185*
- Treatment Recommendations for Selective NTM in Adults and Children *187*

***Mycobacterium leprae* Infection 190**
- Microbiological Aspects *190*
- Clinical Manifestations *190*
- Current Trends of Leprosy in India and Global Context *190*
- Laboratory Diagnostics Including Immunologic Testings *191*
- Drug Treatment and Resistant Aspects *192*
- Lepra Reaction and its Management *192*
- Contacts of Leprosy and Post-exposure Prophylaxis to Household or Group Residents *193*
- Vaccines: Current Status and Future Prospects *193*
- Case Management Under Special Circumstances *194*
- Appendices *194*

15. Infective Endocarditis and Pacemaker Infections (Childhood-Adolescent-Adults) 195
- Background Information (Key Points) *195*
- Modified Duke Clinical Criteria for Diagnosis *196*
- Microbiology Blood Cultures: Evidence Based *197*
- Pediatrics Aspects (Children and Newborn Infants) *198*

JAYPEE BROTHERS

- Pathogen-Specific Treatment of Native Valve Endocarditis *199*
- Treatment of Prosthetic Valve Endocarditis *200*
- Permanent Pacemaker and Implantable Cardioverter-Defibrillator Infections *201*
- Recommended Prophylactic Regimens *203*

16. Infectious Diarrhea 204
- Clinical and Epidemiologic Outlines *204*
- Bacterial *206*
- Viral Gastroenteritis *218*
- Norovirus (Norwalk-like Virus) and Sapovirus Infections *218*
- Parasitic Diarrheal Infections *219*

17. Urinary Tract Infections in Childhood and Adults 221

Pediatric Urinary Tract Infection 221
- Urinary Tract Infection in Children: Knowledge Updates *221*
- Urinary Tract Infection Terminology *222*
- Basics *222*
- Urinalysis and Culturing Aspects *222*
- Role of Imaging Studies *224*
- Treatment: Drugs and Dosages *224*
- Children with Cystitis *225*
- Emergence of Extended-Spectrum-Beta-Lactamase-Producing Enterobacteriaceae *225*

Adults' Urinary Tract Infection 226
- Clinical Backgrounds *226*
- Uropathogens: Prevalence and Frequency *226*
- Practical Management: General Guideline *227*
- Acute Cystitis *229*
- Acute Prostatitis *230*
- Acute Pyelonephritis *230*
- Drug Therapy with a Urinary Catheter *231*
- Role of Oral D-Mannose Supplements for Urinary Tract Infections *233*

Appendices 233
- Resistant Urinary Tract Infection Pathogens (Hospital and Community Acquired)– The KIMS Hospital Thiruvananthapuram (2016–2017) *233*

18. Bone and Joint Infections 234
- Bone and Joint Infections *234*
- Acute Osteomyelitis in Children and Adults and a Case Scenario *235*
- Vertebral Osteomyelitis, Diskitis and Epidural Abscess *237*
- Spinal Tuberculosis: Diagnosis and Treatment (Pott's Disease) *238*
- Prosthetic Joint Infections *239*
- Diabetes Mellitus: Associated Osteomyelitis *240*

19. Clinical Virology (Systemic Viral Infections) 242

Respiratory Viruses 242
- Clinical Virology Overview *242*
- Measles and Rubella *244*
- Viruses Associated Acute Respiratory Tract Infections *245*
- Influenza Viruses (Flu) *246*
- Human Coronaviruses, Including Severe Acute Respiratory Syndrome, Middle-East Respiratory Syndrome Coronavirus *255*

JAYPEE BROTHERS

- Respiratory Syncytial Viruses *260*
- Human Metapneumovirus *262*
- Human Bocavirus *263*
- Nipah Virus Outbreak Associated with Severe Encephalitis and Respiratory Illnesses *263*

Hepatotropic Viruses 264

- Hepatotropic Viruses (Type A, B, C, D and E) *264*

Other Herpes Viruses 281

- Herpesviridae *281*
- Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome *294*
- Ebola and Marburg Viruses: Hemorrhagic Fevers by Filoviruses *298*

Approved Antiviral Drugs 300

- Pharmacologic Basis of the Antiviral Drugs *300*
- Clinical Utility of Drugs Based on Specific Non-HIV Viral Diseases *304*
- Antiviral Drug against Smallpox Virus (Tecovirimat) *306*
- Drug Prescription and Precautions *306*

20. Systemic Fungal Diseases and Antifungal Drugs (Candidiasis/Aspergillus/Mucormycosis/Cryptococcosis/Blastomycosis/Histoplasmosis/Coccidioidomycosis/Sporotrichosis) 307

- Systemic Diseases: Management Guidelines *307*
- Antifungal Drugs in General *307*
- Other Modern Antifungal Drugs *309*
- Systemic Diseases and Antifungal Drug Dosages *311*
- Antifungal Susceptibility Testing *316*

21. Parasitic Diseases and Drugs 317

- General Dictum *317*
- Giardiasis: *Giardia intestinalis* (Formerly *Giardia lamblia* and *Giardia duodenalis* Infections) *317*
- Amebiasis *318*
- Cryptosporidiosis *320*
- Leishmaniasis *321*
- Toxoplasmosis *321*
- Schistosomiasis and Fascioliasis *323*

22. Febrile Neutropenia (Adults and Pediatric Perspective) 326

- Febrile Neutropenic Risks *326*
- Empiric Therapy: Evidence Based with Grades of Recommendation *327*
- Chemoprophylaxis Drug Regimen for Patients with Expected Prolonged Neutropenia *330*
- Antimicrobial Prophylaxis for Neutropenic Cancer Patients *331*
- Approach to Febrile Neutropenia in the General Pediatric Setting *332*

23. Infections in Transplant Recipients 335

- Background and Transplant Resources: Solid Organs, Bone Marrow, Umbilical Cord and Peripheral Blood *335*
- Pathogens Responsible In Transplant Infections *338*
- Immunosuppressive Drugs (Antirejection Drugs in Transplant Recipients) *338*
- Post-transplantation Infections (Timeline, Type of Transplant and the Type of Pathogen Infected) *340*
- Prevention of Bacterial Infections in Transplant Recipients *341*
- Approach to Patient and Pathogen Specific Management *341*
- Vaccination Aspects and Recommendations (Recommended Immunization for Immunocompromised Persons) *353*

JAYPEE BROTHERS

24. Obstetrical Infections (Pregnant Women, Fetus and Newborn).....354

Maternal Infections in Pregnancy 354

- Understanding Infections in Pregnancy *354*
- Maternal and Neonatal Group B *Streptococcus* Infections *355*
- Listeriosis *(Listeria monocytogenes) 360*
- Gynecologic and Sexually Transmitted Infections *361*
- Urinary Tract Infections in Pregnancy *370*
- Tuberculosis and its Effect in Pregnancy (Maternal Tuberculosis Disease) *371*

Congenital Infections: Viral and Parasitic (Maternal and Fetal Outcomes in Pregnancy) 373

- Maternal: Fetal and Newborn Transmission *373*
- Congenital Cytomegalovirus Infection *374*
- Congenital Cytomegalovirus Interactive Case Scenario *381*
- Human Immunodeficiency Virus in Pregnant Women (Mother-to-Child Transmission) *381*
- Hepatotropic Viruses (HBV, HCV and HEV) *382*
- Maternal and Congenital Rubella *387*
- Parvovirus B19: Congenital Infections *389*
- Pregnant Women and Influenza *390*
- Maternal and Neonatal Herpes Simplex Virus Infection *390*
- Varicella-Zoster Virus Congenital and Neonatal (Perinatal) Varicella *392*
- Zika Virus Infection and Pregnancy Outcomes *394*
- Congenital Chikungunya Virus *401*
- Parasitic Infections *401*

25. Infectious Diseases in Dentistry and Dental Healthcare Settings (Preventing Disease Transmission in Dental Care Settings).....408

- Infection Prevalences in Dentistry *408*
- Recommended Infection Control Aspects *409*
- Factors that Predisposes to Endocarditis *409*
- Awareness and Acceptance of Hepatitis B Immunization *410*
- Dental Prophylaxis versus Oral Hygiene and Disease Prevention (Recommended Dental Antibiotic-Prophylactic Regimens) *410*
- Pediatric and Adolescent Antibiotic Therapy Guideline *411*
- Dental Trauma and Oral Wound Management *414*
- Oral Cancer Tumorigenesis *415*

26. Recurrent Infections due to Immune Deficiencies.....416

- Clinical Guide to Identify Patients with Immunodeficiency *416*
- Primary Humoral Immunodeficiency *417*
- Cellular, Complement and Phagocytic Dysfunctions and Disorders *418*
- Therapeutic Principles *420*
- A Case Challenge: Recurrent Infections in A 5-Year-Old Boy *420*

27. Microbiome (Human Microbiome in Health and Disease).....421

- Microbiota versus Microbiome versus Biofilm *421*
- Benefits of the Gut's Normal Flora (Gut Microbiome) *422*
- Hospital Microbiota and Microbiome *422*
- Gut Dysbiosis and the Microbiome *422*
- Clinical Implications and Therapeutic and Preventive Opportunities *423*
- Glossary *424*

JAYPEE BROTHERS

28. Hospital-acquired Infections and Healthcare-associated Infections 425
- Definitions *425*
- Hospital-acquired Infections: Global and National Status *425*
- Important Hospital-acquired Infection Anatomical Sites and Prevention Strategies *427*
- Specific Prevention Aspects: BSI, CAUTI, SSI, VAP/HAP *429*
- Mobile Handheld Devices and Healthcare-associated Infections *433*
- Antimicrobial Resistance: General Infection Control Measures *433*
- Multidrug-Resistant Organisms: Role in Hospital-acquired Infections Control—Regional (KIMS Hospital) Status *434*
- Infection Control and Isolation Considerations for the Pediatric Practitioner *437*
- The Role of Personal Protective Equipment and Prevention of Spread of Infection in the Healthcare Setting *438*

29. Therapeutic Antibodies for Infectious Diseases [Polyclonal Immune Globulin Intravenous (IGIV) and Monoclonal Antibodies (mAbs)] 440
- Therapeutic Uses: Historical Aspects *440*
- Types of Polyclonal Intramuscular, Intravenous and Subcutaneous Immunoglobulins *441*
- Monoclonal Antibodies for Infectious Diseases *445*
- Anti-tumor Necrosis Factor Antibody Therapeutic Products *447*
- Anti-interferons Antibodies *448*
- Stem Cells (Mesenchymal Stem Cells) Uses in Infectious Diseases *448*

30. Vaccinology (Principles and Practices: An Essential Guide) 450
- An Overview: Pediatrics and Adults Vaccination *450*
- Immunization Success Stories *452*
- Vaccine Highlights and Remarks *453*
- Combination Vaccines (Combos) *466*
- Adverse Events of Vaccines *468*
- Travel Vaccination *468*
- Vaccines for the Elderlies (65 Years of Age and Older) *469*
- Immunization during Pregnancy (Maternal Immunization) *470*
- Immunization in Special Clinical Circumstances: Immunocompromised or Kidney Dialyzing Patients or Transplant Recipients *472*
- Cancer Vaccines: A Novel Approach to Cancer *478*
- Leprosy Vaccine Development *478*
- Vaccine Myths and Misconceptions *479*
- Appendices: Recommended Immunization Schedules AAP/ACIP and IAP/ACVIP *482*

Index *489*

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19

Clinical Virology
(Systemic Viral Infections)

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Chapter Outline

Respiratory Viruses
- Clinical Virology Overview
- Measles and Rubella
- Viruses Associated Acute Respiratory Tract Infections
- Influenza Viruses (Flu)
- Human Coronaviruses, including Severe Acute Respiratory Syndrome, Middle-East Respiratory Syndrome Coronavirus
- Respiratory Syncytial Viruses
- Human Metapneumovirus
- Human Bocavirus
- Nipah Virus Outbreak Associated with Severe Encephalitis and Respiratory Illnesses

Hepatotropic Viruses
- Hepatotropic Viruses (Type A, B, C, D and E)

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- Ebola and Marburg viruses: (Hemorrhagic Fevers by Filoviruses)

Approved Antiviral Drugs
- Approved Antiviral Drugs
- Pharmacologic Basis of the Antiviral Drugs
- Clinical Utility of Drugs Based on Specific Non-HIV Viral Diseases
- Antiviral Drug against Smallpox Virus (Tecovirimat)
- Drug Prescription and Precautions

RESPIRATORY VIRUSES

CLINICAL VIROLOGY OVERVIEW

Viruses are living organisms that cannot replicate without a host cell. Viruses do not contain a ribosome, so they cannot make proteins. They are the only type of microorganism that cannot reproduce without a host cell. This makes them totally dependent on their host. They can infect animals, plants, fungi and even bacteria. Almost every ecosystem on earth contains viruses. Viruses have different shapes and sizes and they can be categorized by their shapes. Before entering a cell, viruses exist in a form known as virions, roughly one-hundredth the size of a bacterium and consist of two or three distinct parts (Fig. 19.1):

- Genetic material, either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) (*depends on whether they use DNA or RNA to replicate*)

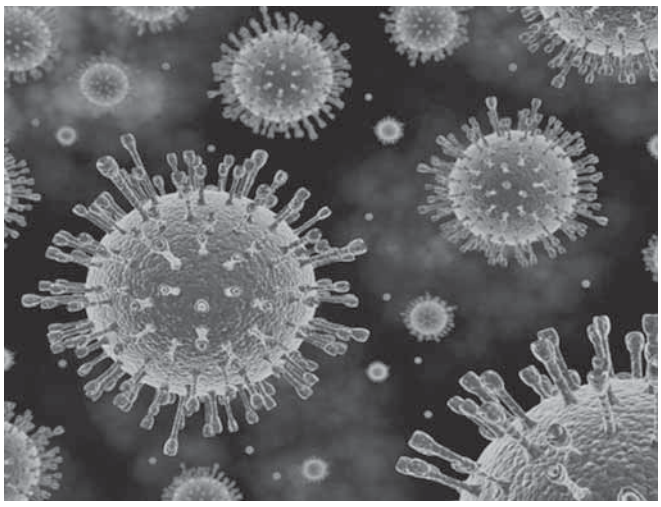

Fig. 19.1: Viruses photographed with a transmission electron microscope.
Source: Concise ID book 2017 cover page published by the New Delhi Publisher JP.

- A protein coat, or capsid, which protects the genetic information
- A lipid envelope is sometimes present around the protein coat when the virus is outside of the cell.

RNA viruses replicate within the cytoplasm. Exceptions are known to this rule—poxviruses replicate within the cytoplasm and orthomyxoviruses and hepatitis D virus (RNA viruses) replicate within the nucleus. Molecular techniques are used to compare the DNA and RNA of viruses and find out more about where they come from *http://www.virology.ws/2009/02/13/acute-viral-infections/*.

Mostly in-apparent infection: Very often an acute viral infection may cause little or no clinical symptoms, called as asymptomatic—in apparent infection. During an in apparent infection, sufficient virus replication occurs in the host to induce antiviral antibodies, but not enough to cause disease. A well-known example is hepatotropic viruses, poliovirus and many respiratory tract infections—over 90% are without symptoms.

Symptomatic acute infections begin with an incubation period (IP), during which the genomes replicate and the host innate responses are initiated. The cytokines produced early in infection lead to classical symptoms of an acute infection—aches, pains, fever, malaise and nausea. Some IPs are as short as 1 day (influenza, rhinovirus), indicating that the symptoms are produced by local viral multiplication near the site of entry. For some infections, IPs can last many days (papilloma, 50–150 days) or even years [acquired immunodeficiency syndrome (AIDS), 1–10 years)]. In these infections, the symptoms are likely produced by virus- or immune-induced tissue damage far from the site of entry, e.g. immune-mediated viral encephalomyelitis.

Acute viral infections are responsible for epidemics of disease involving millions of individuals each year, such as influenza and measles. When vaccines are not available, acute infections are difficult to control. The rapid clearance of acute viral infections is a consequence of robust host defenses. The same virus may cause a long-term or persistent infection, in immunocompromised hosts. An example is Norovirus infection, which is self-limiting in immunocompetent hosts, but causes a chronic infection in immunosuppressed kidney transplant recipients. Readers are directed to see Chapter 23; Infections in Transplant Recipients.

General diagnosis and treatment: Viral disease is usually detected by clinical presentation, for instance febrile onset with progressive skin rash, respiratory symptoms, adenitis (measles, rubella, etc.) muscular and joint pains preceding and or associated with fever and rash (dengue, chikungunya, Zika, etc.). Laboratory investigation is not directly effective in detecting viral infections, because the illness are commonly of limited duration and antibody responses are detected after clinical recovery, in many cases.

Specific viral infection can now easily be detected with the newly available automated nested multiplex polymerase chain reaction (PCR) technology; the FilmArray® system for detecting respiratory central nervous system (CNS) and gastrointestinal tract (GIT) viral and bacterial pathogens. The FilmArray Respiratory Panel (RP) system uses a molecular syndromic approach to accurately detect and identify a wide range of pathogens—not just flu A and flu B. Because a large number of pathogens cause respiratory infections, tests that only identify flu A and flu B run the risk of missing the real culprit. The FilmArray RP system provides an accurate, comprehensive alternative to targeted influenza testing and will detect a greater number of pathogens no matter the season or the time of year.

Treatment usually consists in reducing the symptoms; antipyretic and analgesic drugs are commonly prescribed. Antibiotics are not effective against viral infections, but if a person has a bacterial infection in addition to a viral infection, an antibiotic is often necessary.

There are no effective antiviral drugs for many viral infections. However, there are several drugs for influenza, one or more herpes viruses [Herpes simplex virus, varicella-zoster virus, Cytomegalovirus (HSV, VZV, CMV, etc.)] and many new antiviral drugs for treatment of human immunodeficiency virus (HIV) and hepatitis B and hepatitis C viruses. Antiviral drugs can work by:

- Interfering with the replication of viruses
- Strengthening the immune response to the viral infection.

Basically, the antiviral drugs are much more difficult to develop than antibacterial drugs. Also, unlike antibiotics, which are usually effective against many different species of bacteria, most antiviral drugs are usually effective against only one (or a very few) viruses. Antiviral drugs can be toxic to human cells. Also, viruses can develop resistance to antiviral drugs. Other antiviral agents can

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strengthen the immune response to the viral infection. These drugs include several types of interferons (IFNs), immunoglobulins (Igs) and vaccines:

- IFN drugs are replicas of naturally occurring substances that slow or stop viral replication
- Immunoglobulin is a sterilized solution of antibodies (also called immunoglobulin) collected from a group of people. These include general immunoglobulin (Intramuscular IM and Intravenous immunoglobulin-IVIG) and species-specific immunoglobulin against varicella zoster virus (VZIG), hepatitis B immunoglobulin (HBIG), respiratory syncytial virus immunoglobulin (RSVIG), CMV immunoglobulin (CMVIG), etc.
- Vaccines are materials that help prevent infection by stimulating the body's natural defense mechanisms (*Readers are directed for details in Chapter 30 Vaccinology)*.

MEASLES AND RUBELLA

A highly contagious febrile exanthematous illness; 90% of susceptible household contacts of a person with measles will become infected. When these infections happen anywhere in the world, it can travel and spread too many countries. Measles is a leading cause of death among children around the world. Complications from measles are more common among adults including pneumonitis, hepatitis, encephalitis, optic neuritis, etc.

In India, nationwide exact-data are not available regarding the prevalence of measles and rubella infection. The global estimates for the year 2013 suggest that close to 0.14 million deaths were attributed to measles, accounting 400 children dies every day, 16 every hour despite the fact that a safe and effective vaccine has been available for over 50 years. Study findings have indicated that:

- More than 50% of the global measles-associated deaths were reported in India alone (*Vaccine 2013*;31:4655-61) of the 134,000 measles deaths globally in 2015, an estimated 47,000 occurred in India
- 400 children die every day, 16 every hour despite the fact that a safe and effective vaccine has been available for over 50 years
- Likewise rubella is endemic, both acquired and congenital rubella infections are highly prevalent despite measles, mumps and rubella (MMR) vaccine availability as a part of routine childhood immunization (*BMJ 2014;349:g4844*).

Measles: Globally measles remains one of the leading causes of death among young children even though a safe and cost-effective vaccine is available. A highly contagious febrile exanthematous illness and 90% of susceptible household contacts of a person with measles will become infected. When these infections happen anywhere in the world, it can travel and spread to many countries. Complications from measles are more common among adults.

According to new data from the WHO (Nov 26, 2018), measles cases surged in 2017, as multiple countries experienced severe and prolonged outbreaks of the disease due to gaps in vaccination coverage. The resurgence of measles is of serious concern, with extended outbreaks occurring across regions and particularly in countries that had achieved or were close to achieving measles elimination.

Rubella is generally a mild illness but when pregnant women become infected, there is 90% chance of the fetus having congenital rubella syndrome (CRS). The baby can be born with multiple birth defects; if it survives, these infants are with developmental delay with mental and intellectual disability. Currently, 100,000 babies are born with CRS around the world each year.

Since 1963, measles and rubella has been a vaccine-preventable disease. In many industrialized countries including Middle-East, European regions, a highly effective vaccination program led to an over 99% reduction. Sustained by the elimination of polio 6 years ago and maternal and neonatal tetanus in 2016, India has set an ambitious target of eliminating measles and controlling CRS, caused by the rubella virus, by 2020.

An on going surveillance activity in the Kerala Institute of Medical Sciences (KIMS), Thiruvananthapuram indicates both measles and rubella illness occur continually. The population of pregnant women who are at risk to develop rubella studied in 2013 and 2014 in Thiruvananthapuram metropolitan city were 36% and 22%, which is high *(Pawan Wagle et al. August, New Delhi, CIDSCON)*. Hence, all reproductive age group women have to be screened for rubella immunity (rubella IgG positivity) and booster dose of rubella vaccine is recommended for those who are nonimmune (negative rubella IgG test), to reduce incidence of CRS in India.

Best protection against measles is to get vaccinated and have received all recommended doses of measles or MMR or MMRV (measles-containing vaccine—MCV), before travelling internationally. The MMRV is not licensed for children younger than 12 months.

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Consider international travelers without presumptive evidence of measles immunity to be at risk for measles. Those who have no contraindications to MCV should receive MCV before they travel. For infants aged 6–11 months, administer one MCV dose.

Role of standard immunoglobulin in measles susceptible individuals; GamaSTAN® is the only immunoglobulin product available to protect against measles. Intramuscular GamaSTAN® can be used for prevention or modification of measles in susceptible individuals exposed fewer than 6 days previously.

VIRUSES ASSOCIATED ACUTE RESPIRATORY TRACT INFECTIONS

Viral infections commonly affect the upper or lower respiratory tract. These infections are generally classified clinically according to syndrome (Table 19.1). Severity of viral respiratory illness varies widely; severe disease is more likely in the elderly and infants. Morbidity may result directly from viral infection or may be indirect, due to exacerbation of underlying cardiopulmonary conditions or bacterial superinfection of the lung, paranasal sinuses or middle ear.

The *BioFire FilmArray*, Pneumonia Panel (PP) tests can identifies the most common viral and bacterial respiratory pathogens that present with nearly indistinguishable signs and symptoms. Also, detects antimicrobial resistant genes directly from lower respiratory specimen in about one hour from the time of specimen collection.

The Pneumonia Panel set menu include the following:

Viruses (Qualitative)

- Adenovirus
- Coronavirus HKU1
- Coronavirus NL63
- Coronavirus 229E
- Coronavirus OC43
- Human Metapneumovirus (hMPV)
- Human Rhinovirus/Enterovirus
- Influenza A
- Influenza A/H1
- Influenza A/H3
- Influenza A/H1-2009
- Influenza B
- Parainfluenza Virus-1
- Parainfluenza Virus-2
- Parainfluenza Virus-3
- Parainfluenza Virus-4
- Respiratory syncytial virus (RSV).

Bacteria (Semiquantitative)

- *Acinetobacter calcoaceticus baumannii* complex
- *Enterobacter cloacae* complex
- *E. coli*
- *Bordetella pertussis*
- *Haemophilus influenzae*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Klebsiella pneumonia* group
- *Moraxella catarrhalis*
- *Proteus* spp.
- *Pseudomonas aeruginosa*
- *Serratia marcescens*
- *Staphylococcus aureus*
- *Staphylococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes.*

Atypical bacteria (Qualitative)

- *Chlamydophila pneumoniae*
- *Legionella pneumonia*
- *Mycoplasma pneumoniae.*

Table 19.1: Virus-associated clinical respiratory syndromes.

Syndrome	*Commonly-associated viruses*	*Less commonly-associated viruses*
Cold and Coryza	Rhino and Corona viruses	Influenza and parainfluenza viruses, Enterovirus and adenoviruses
Influenza (flu)	Influenza (flu) viruses	Parainfluenza and adenoviruses
Croup	Parainfluenza viruses, H1N1 swine flu v, the H3N2 strains, etc.	Influenza, respiratory syncytial virus and adenoviruses
Bronchiolitis	Respiratory syncytial virus	Influenza, parainfluenza and adenoviruses
Bronchopneumonia	Influenza, respiratory syncytial virus, adenoviruses	Parainfluenza, measles, varicella zoster-virus and Cytomegalovirus

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Resistant markers

- Carbapenemase (IMP, KPC, NDM, Oxa48-like, VIM)
- ESBL (CTX-M)
- MRSA (mecA/C and MREJ).

The respiratory viral pathogens prevalence among patients hospitalized in KIMS, Thiruvananthapuram between September 2016 through December, 2017 is summarized and tabulated in Table 19.2.

The KIMS hospital Thiruvananthapuram, Infection Control Committee surveillance reveals that patients are admitted round the year for lower respiratory tract infections due to viruses of varied etiology. Community acquired respiratory infections are highly significant, with peak viral activities during summer and the South-West monsoon periods. Our regional clinical experiences and the evolving epidemiologic observations over the last 5 years period reiterate the fact that; the timing, severity and length of the virus season varies from 1 year to another. Not only the flu virus but also other pathogens such as RSV and hMPV viruses circulate concurrently causing clinical severity among vulnerable, e.g. pediatrics and geriatric population with severe morbidity and death.

INFLUENZA VIRUSES (FLU)

Influenza (also known as the flu) is a contagious respiratory illness caused by flu viruses. Most people who get the flu will have mild illness, will not need medical care or

Table 19.2: Rapid multiplex PCR BioFire tests confirmed cases of acute respiratory illnesses among hospitalized patients (September 2016 to August 2017).

Month/year	*Positive LRTI/ Tested number (%)*	*Flu % of the LRTI*	*Pathogens*
September 2016	11/19 = 58%	18%	Flu B – 02/respiratory syncytial virus (RSV) – 04/human metapneumovirus (hMPV) – 01/ rhino and Enterovirus-04
October	06/16 = 38%	17%	Flu B – 01/RSV – 01/hMPV – 01 Adenovirus – 02/Coronaviruses (CoV) – 01
November	08/17 = 47%	13%	Flu B – 01/Rhino and Enterovirus – 05 Adenovirus – 02
December	05/14 = 36%	20%	Flu B – 01/hMPV – 01/rhino and Enterovirus – 03
January 2017	05/19 = 26%	40%	Flu A–02 /hMPV and Enterovirus – 01 Adenovirus– 01/CoV and Mycoplasma pneumoniae 01
February	17/37 = 46%	88%	Flu A – 13/flu B – 01/flu A and hMPV and Enterovirus 01 Adenovirus – 02
March	23/45 = 51%	65%	Flu A – 02/flu A H1 – 09/flu B – 01/hMPV – 02/rhino and Enterovirus – 01 parainfluenza 3 – 02
April	17/31 = 55%	71%	Flu A–02/flu A H1–09/flu B–01/hMPV–02/rhino and Enterovirus–01 parainfluenza 3–02
May	15/31 = 48%	60%	Flu A – 03/flu A H1– 06/parainfluenza 3 – 01 Adenovirus – 02 Rhino/Enterovirus – 01/Rhino + Entero + CoV – 01 Bordetella pertussis – 01
June	24/42 = 58%	71%	Flu A – 04, flu H3 – 02, Flu A H1 – 09, Flu H3, Rhino, Entero –01, Flu H1, Entero, Rhino – 01, hMPV – 01, Entero Rhino – 06
July	32/53= 60%	81%	Flu A – 02, Flu H1 – 11, Flu H3 – 12, Rhino, Enterovirus, Flu A H3 – 01, Adenovirus – 01, hMPV – 01, CoV – 02, Rhino, Enterovirus – 01, hMPV, Enterovirus, Rhino – 01
August	18/31 = 58%	28%	Flu A – 01, Flu A H1 – 02, A H3 – 02, CoV – 01, HMPV – 05, RSV – 03, Rhino Enterovirus – 03, B. pertussis – 01

September 2016 to August 2017: Of the 355 viral PCR tested, 181 tests (51%) were positive for respiratory viruses. Of the 181 positive viral PCR 110 (58%) are flu viruses. Other dominant viruses are hMNV 20 cases and 8 RSV cases.

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antiviral drugs and will recover in less than 2 weeks. However, clinical symptoms are typically more severe than other respiratory viral-cold syndromes; consisting of myalgias, headaches, occasional gastrointestinal symptoms, as well as fever, cough, nasal congestion and pharyngitis. The IP is 1–4 days. The more common complication of influenza is pneumonia, occurring in patients with underlying chronic illnesses. Individuals who are at high risk of developing serious flu-related complications includes people 65 years and older, people of any age with certain chronic medical conditions (such as asthma, diabetes, or heart disease), pregnant women and young children. Fatal outcomes, including sudden death, have been reported in both chronically ill and previously healthy children.

- The best way to prevent the flu is by getting vaccinated each year.

In essence the type of influenza infections are broadly categorized as:

- Seasonal annual event type
- Pandemic type
- Avian flu, swine or variant and others like
- Bat and Canine flu infection.

Flu viruses have a single-stranded segmented RNA genome belong to the family orthomyxoviridae and are classified into types A, B and C on the basis of their core proteins. Type A viruses are further subdivided according to their envelope glycoproteins with hemagglutinin (HA) or neuraminidase (NA) activity. Flu B and flu C viruses mainly affect humans, whereas flu A viruses infects a range of mammalian and avian species. Only type A and type B cause human disease of any concern (Fig. 19.2).

- Enveloped glycoprotein virus, with HA and neuraminidase spikes (NA) activities
- Three types: A, B and C
- Type A undergoes antigenic shift and drift
- Type B undergoes antigenic drift only and type C is relatively stable.

Characteristic of many RNA genome viruses, flu virus undergoes high mutation rates and frequent genetic reassortment (combination and rearrangement of genetic material) leading to variability in HA and NA antigens. Minor changes in the protein structure in influenza A strains ("antigenic drift") occur frequently, enabling the virus to cause repetitive influenza outbreaks by evading immune recognition. Major changes in the influenza type A, HA antigen ("antigenic shift") are caused by



Fig. 19.2: Electron microscopic view of flu virus. (*Courtesy*: Medscape 2015)

reassortment from different influenza A subtypes, such as between animal and human subtypes and in rare events, such shifted viruses can result in strains capable of causing large regional or global pandemic outbreaks.

Past antigenic shift and the clinical consequences:

- 1918–1919 H1N1 "Spanish influenza" 50–100 million deaths
- 1957 H2N2 "Asian flu" 1–2 million deaths
- 1968 H3N2 "Hong Kong flu" 700,000 deaths
- 1977 H1N1 Re-emergence No pandemic
- 2009–2010 H1N1 "Swine flu Mild pandemic
- 2017–2018 Elevated flu activity, mostly H3N2 strain
- At least 15 HA subtype and 9 NA subtypes occur in nature. Up until 1997, only viruses of H1, H2 and H3 are known to infect and cause disease in humans.

The Spanish influenza of 1918–1919, a pandemic flu estimated to have infected more than 500 million people worldwide, likely caused between 50 million and 100 million deaths globally. In the United States alone, the Spanish flu devastated families, businesses and communities, leaving approximately 670,000 Americans dead in its wake. In reality, 100 years after the deadly Spanish flu, the possibility of a pandemic threat, such as the H1N1 Spanish flu cannot be repeated because of its time and place in history that medical science and public health have so advanced in the intervening years. Yet, in the face of that threat, people remain dangerously vulnerable despite the advent of drugs, protocols and vaccines available to treat the flu and associated infections.

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(*Barry JB. How the horrific 1918 flu spread across America. Smithsonian Magazine. November 2017. Available at: https://www.smithsonianmag.com/history/journal-plague-year-180965222*).

A sneeze captured on high-speed video. After a sneeze, large droplets of saliva and mucus (green) shoot out of the mouth, but fall relatively quickly. A turbulent cloud carries smaller droplets (red) and allows them to drift for up to 8 meters (Fig. 19.3).

Many of the larger droplets can travel up to 8 meters for a sneeze and 6 meters for a cough, depending on the environmental conditions and stay suspended for up to 10 minutes—far enough and long enough to reach someone at the other end of a large room, not to mention the ceiling ventilation system. (*Bourouiba L, Dehandschoewercker E, Bush JWM. The snot-spattered experiments that show how far sneezes really spread. J Fluid Mech. 2014;745:537-63*).

An influenza virus particle, or virions spread up to 6 feet through large respiratory droplets from coughing, sneezing, or talking, but they can also be spread via contaminated surfaces. The infection is transmissible for over 24 hours before the onset of symptoms and 30% or more of flu shedders are asymptomatic altogether. An influenza pandemic is a rare but a recurrent event. Seasonal outbreaks occur all over the world, with an annual global attack rate estimated at 5–10% in adults and 20–30% in children. When flu outbreak has been documented in the community, a clinical diagnosis can be made based solely on signs and symptoms.

The global circulation patterns of seasonal flu viruses are well characterized and vary with antigenic drift. The

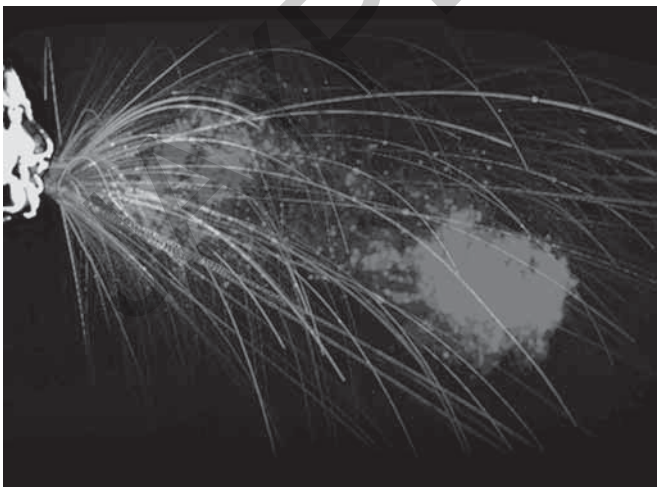

Fig. 19.3: Viral transmission during coughing and sneezing. (*Courtesy*: Smithsonian magazine 2018)

circulation patterns of A/H1N1 (up to 2009), B/Victoria and B/Yamagata viruses differ substantially from those of A/H3N2 viruses. While genetic variants of A/H3N2 viruses did not persist locally between epidemics, genetic variants of A/H1N1 and B viruses persisted across multiple seasons and exhibited a limited role in disseminating new variants.

The less frequent global movement of influenza A/H1N1 and influenza B viruses coincided with slower rates of antigenic evolution, lower ages of infection (childhood infections) and smaller less frequent epidemics compared to A/H3N2 viruses.

(*Trevor Bedford, Steven Riley, et al. Global circulation patterns of seasonal influenza viruses vary with antigenic drift. Nature. 2015;523(7559):217-20. Published online 2015 Jun 8*).

- In general community flu virus activity and annual peaks are variable; the clinical severity and the dominant viral strain for a season are unpredictable beforehand
- The first established influenza season of the year 2015 in the Thiruvananthapuram metropolitan city of Kerala state is shown in Figure 19.4
- Annual dissimilarity in climate variables is more important than their absolute values for determining their effect on the viral seasonality
- During 2018 vigorous southwest monsoon activities in Kerala state that has resulted a drastically change in a seasonality pattern in the region. Hospitalized and confirmed admitted influenza cases are few or none during the peak seasonal months and this may be the result of the extreme rains and winds that are *not conducive* for influenza virus survivals.

The clinical and the circulating flu virus pattern including seasonality aspect over a 5 year period has been described in Table 19.3 (*KIMS Hospital Infection Control committee surveillance data compiled by IC Officer Ms. Aisha-March 2018*).

- In the entire year of 2017, a total of 348 plus individuals, (predominantly adults) suspected to have clinical flu illness. Thirty two percent of these 110 cases are positive for A/H1N1, A/H3N2 virus strains
- The flu activity and the hospitalization rate during the year 2017 has been several fold higher than the previous year
- Virus activities increases during summer months (February–July), reaching a peak incidence in the

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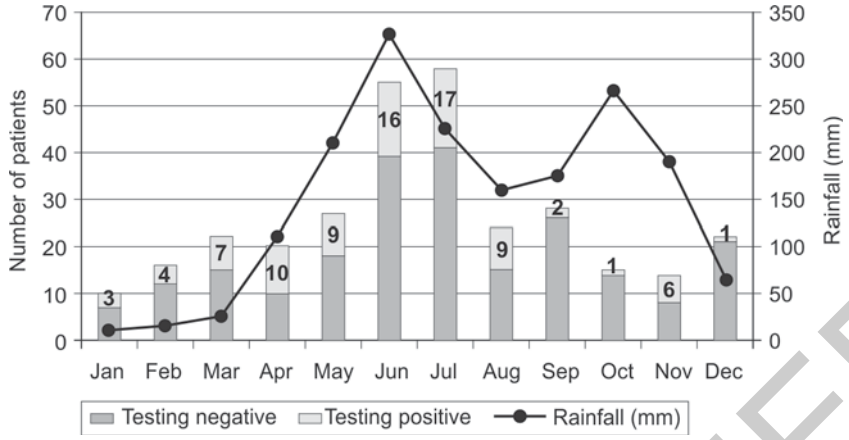

Fig. 19.4: 2017 Thiruvananthapuram flu season; selective meteorological (rainfall) features, distribution of influenza cases hospitalized at KIMS and the positive specimens for H1N1 PCR testing during January through December 2015. (Sahadulla MI, Uduman SA, et al. Illustration courtesy of Concise ID Handbook. 2017).

Table 19.3: Clinical and virologic surveillance aspects of flu viruses that are seen in Kerala Institute of Medical Sciences (KIMS) hospital, Thiruvananthapuram over a 5 year period (2013–2017—reported cases to Department of Health).

Months	*2013 positive/ number tested (%)*	*2014 positive/ number tested (%)*	*2015 positive/ number tested (%)*	*2016 positive/ number tested (%)*	*2017 positive/ number tested (%)*	*Kerala weather (RH%)*
January	0/2 (0)	0/2 (0)	3/10 (30)	–	2/19 (11)	Winter
February	0/9 (0)	0/0 (0)	4/16 (25)	–	15/37 (46)	Winter
March	2 /4 (50)	0/0 (0)	7/22 (32)	–	15/45 (33)	Spring
April	0/6 (0)	1/2 (50)	10/20 (50)	05	12/31 (39)	Summer
May	0/8 (0)	1/2 (50)	09/27 (33)	04	09/31 (29)	Summer
June	0/5 (0)	1/12 (8)	16/55 (29)	17	17/42 (40)	Southwest summer monsoon
July	2/5 (40)	0/8 (0)	17/58 (29)	05	26/53 (49)	Southwest summer monsoon
August	0/10 (0)	0/4 (0)	09/24 (38)	15	05/31 (16)	Southwest summer monsoon
September	0/3 (0)	0/9 (0)	02/28 (7)	1/2	03/33 (9.0)	Fall, autumn
October	0/3 (0)	0/2 (0)	01/15 (7)	89	06/26 (23)	Northeast winter monsoon
November	0/0 (0)	0/1 (0)	06/14 (43)	48	–	Northeast winter monsoon
December	0/7 (0)	0/5 (0)	01/22 (5)	25/106	–	Winter
Total	4/62 (6.5)	3/47 (6.4)	85/311 (27)	–	110 +/348 tested (32%)	–

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Table 19.4: Summary of influenza diagnostic tests.

Influenza diagnostic test	*Method*	*Availability*	*Turnover time*	*Sensitivity*	*Differentiates flu A virus subtypes*
Rapid diagnostic tests[a]	Antigen detection	Wide	<15 min	10–70%	No
Rapid molecular assays[b]	RNA detection	Wide	<20 min	86–100%	No
Nucleic acid amplification tests (including RT-PCR)	RNA detection	Limited	1–8 h	86–100%	Yes
Direct and indirect immuno-fluorescence assays	Antigen detection	Wide	1–4 h	70–100%	No
Rapid cell culture (shell vials and cell mixtures)	Virus isolation	Limited	1–3 days	100%	Yes
Viral cell culture	Virus isolation	Limited	3–10 days	100%	Yes

(RT-PCR indicates reverse transcriptase-polymerase chain reaction).
[a]Most rapid influenza diagnostic tests are Clinical Laboratory Improvement Amendments (CLIA) waived.
[b]Some rapid influenza molecular assays are CLIA waived, depending on the specimen.
Source: Adopted and modified from Redbook 2018.

South-West (SW) monsoon period (June, July and August) when there was maximum rainfalls of 320, 325 and 225 mm respectively (Table 19.4)

- Globally, the H3N2 has been the dominant strain starting from 2014 and around round 30% of Thiruvananthapuram flu strains are H3N2 type.

Continuous global surveillance and monitoring data [Centers for Disease Control and Prevention, World Health Organization (CDC, WHO)] show the influenza A virus type has drifted and as a result the 2014–2015 influenza vaccine strain was a mismatch. Despite this mismatch, the vaccine was still beneficial, providing some cross-protection for the 2017–2018 season. Our seasonal observation 2014 through 2018, strongly advocates that the "Timing of annual vaccination" during October month need to be revised in Thiruvananthapuram metropolitan regions. The "annual flu–immunization" should be considered *round the year* and this decision is very justifiable.

- The 2017–2018 flu vaccine, represented changes in the influenza A (H3N2) virus and the influenza B virus as compared with the 2014–15 season.

According to the CDC and National Foundation for Infectious Diseases (NFID), influenza was especially severe in the United States last year (2017–2018 influenza seasons); 900,000 people were hospitalized and 80,000 died. The death toll for children in the 2017–2018 seasons was a record-breaking 180, that number surpassed the previous high of 171 for a nonpandemic influenza season. Older adults and those with chronic conditions, such as heart and lung disease, diabetes and obesity are at high risk for influenza complications; about 70% record–hospitalizations and 90% of deaths last year occurred in those age 65 years and older. Also, the CDC and other agencies understand why the 2017–2018 flu vaccine was relatively ineffective against the strain that caused most of this year's illnesses.

Besides vaccination, other ways to control flu infections are—should treat and prevent infection from spreading include early treatment with antiviral drugs such as Tamiflu and Relenza. Hand washing frequently and covering your mouth when coughing or sneezing practices are equally important.

- Early treatment with antiviral drugs is especially important for children 2 years old and younger, along with adults aged 65 years and older, the CDC says
- Therefore, physicians should aggressively use antiviral drugs in suspected flu patients who are: younger than 2 years old, all pregnant women regardless of trimester and those are 65 years or older, with underlying comorbid conditions such as asthma, diabetes, heart or lung and debilitating CNS diseases and those have a suppressed immune system.

This year season (2018–2019) is particularly worrisome since the predominant strain of influenza A virus circulating in the population is H3N2, known to cause more severe disease. Therefore, it is important to continue administering the influenza vaccine to all eligible individuals, young and old. These include:

- All children older than age 6 months, especially children at high risk for complications, such as those with chronic underlying conditions

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- All eligible adults, especially those who routinely are around children, to help "cocoon" these children against influenza and its complications.

Note: Children younger than age 6 months are not vaccinated against influenza and therefore face increased risk for complications and death.

Although significant advances have been made in the laboratory diagnosis of influenza infection, physicians must be aware that the newer molecular tests are much more accurate compared with the older antigen-based tests. In the final analysis, it will come to a clinical decision whether to treat a patient being evaluated for influenza.

Also, worth serious consideration is chemoprophylaxis for children exposed to or suspected of having influenza. Even in otherwise healthy children, influenza antiviral agents can be considered, especially if the patient is seen within the first 48 hours of illness, when these medications are most effective. There also may be some benefit after the first 48 hours.

Of the five approved influenza antiviral agents, the three neuraminidase inhibitors—oseltamivir, zanamivir and peramivir—should be used to treat influenza infection. The two adamantanes—amantadine and rimantadine—are not useful treatments; influenza A strains have become resistant to them and they are ineffective against influenza B.

Finally, remember that all pregnant women should receive influenza immunization and, if they still become infected, they should be treated with oral oseltamivir. After delivery, they should be separated from their newborns until the mother has received at least 48 hours of oseltamivir, is afebrile for at least 24 hours and has control over her respiratory secretions.

Influenza vaccines: The WHO in collaboration with the CDC reviews the world epidemiological situation twice annually and if necessary recommends new vaccine strain(s) in accordance with the available evidence. In general, seasonal influenza vaccines are trivalent or quadrivalent, containing a mixture of influenza A and influenza B strains thought most likely to circulate in the coming season.

For the 2018–2019 seasons, CDC recommends use of the inactivated influenza vaccine (IIV) or the recombinant influenza vaccine (RIV).

Recent Past Seasonal Flu Virus Events

A, B, C are the types of flu viruses; flu C infection is rare and outbreaks caused by flu B viruses are generally less severe than those caused by A virus. (98% of 2015 strains). It is impossible to clinically differentiate between A and B type infection.

- Outbreaks are an annual event; results from frequent minor antigenic changes *(drifts)* caused by point mutation and recombination events that occur during viral replication (2009 H1N1 pandemic) or antigenic *shifts* by changes in the surface glycoproteins. (H3N2 2015 outbreak)
- 2015 H3N2 strain is currently circulating dominant virus type with more hospitalizations and deaths occurring, especially in older people and young children, than during H1N1- or B-predominant seasons
- The 2014–2015 seasons were moderately severe, with overall high levels of outpatient illness, influenza-associated hospitalization and deaths. Type A (H3N2) viruses predominated overall, with 81% being drifted strains
- Given the unpredictable nature of influenza each season, including the efficacy of a particular vaccine, any licensed and age-appropriate influenza vaccine available should be used
- Antiviral resistance among influenza viruses may emerge and increase with increased use of antiviral oral drugs (neuraminidase inhibitors)
- New agents with different modes of action are under investigation, including favipiravir, DAS181, nitazoxanide and broad-spectrum neutralizing monoclonal antibodies.

The 2017–2018 Influenza Season (USA)

This was a high-severity season, with high levels of outpatient clinic and emergency department visits for influenza-like illness (ILI), high influenza-related hospitalization rates, high numbers of pediatric deaths and elevated and geographically widespread influenza activity across the country for an extended period. Influenza A (H3N2) viruses predominated overall for the season through February 2018; influenza B viruses predominated from March 2018 onward.

The 2017–2018 season ranks as the third most severe since the 2003–2004 season and was the first to be classified as high severity for all age groups. The peak percentage of outpatient visits for ILI was the third highest recorded since the 1997–1998 season. Although the hospitalization rates for children this season did not exceed the rates reported during the 2009 pandemic, hospitalization surpassed rates reported in previous

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high-severity influenza A (H3N2)—predominant seasons. Excluding the 2009 pandemic, the 179 pediatric deaths reported through August 18, 2018, during the 2017–2018 seasons (approximately half of which occurred in otherwise healthy children) are the highest reported since influenza-associated pediatric mortality became a nationally notifiable condition in 2004. Analyses of the influenza A (H1N1) pdm09, influenza A (H3N2) and influenza B (Yamagata lineage) viruses showed that circulating viruses were antigenically and genetically similar to the cell-grown reference viruses representing the 2017–2018 Northern Hemisphere influenza vaccine viruses. Although the overall number of circulating influenza B (Victoria lineage) viruses was low, a substantial amount of antigenic drift from the vaccine reference virus influenza B (Brisbane/60/2008) was observed.

[*Garten R, Blanton L, et al. Update: influenza activity in the United States during the 2017–18 season and composition of the 2018–19 influenza vaccine. MMWR Morb Mortal Wkly Rep. 2018;67(22)*].

2009: H1N1 Pandemic Swine Flu Virus

- Swine flu, also known as 2009 H1N1 type A influenza, is a human disease. People get the disease from other people, not from pigs. The disease originally was nicknamed swine flu because the virus that causes the disease originally jumped to humans from the live pigs in which it evolved
- The virus is a "reassortant"—a mix of genes from swine, bird and human flu viruses. Scientists are still arguing about what the virus should be called, but most people know it as the H1N1 swine flu virus
- The swine flu viruses that usually spread among pigs are not the same as human flu viruses. Swine flu does not often infect people, but the current "swine flu" outbreak is caused by a new swine flu virus that has changed in ways that allow it to spread from person to person–among people who haven't had any contact with pigs.

Avian flu or bird flu (avian influenza): AI H5N1 and AI H7N9.

https://www.medscape.com/viewarticle/887312?src=wnl_edit_tpal&uac=48448CX October 22, 2017.

New H7N9 bird flu strain in China has pandemic potential. The H7N9 virus has been circulating in China since 2013, causing severe disease in people exposed to infected poultry. In 2016, human cases spiked and the virus split into two distinct strains (high and low pathogenic) that are so different they no longer succumb to existing vaccines.

Infection of humans with highly pathogenic avian influenza A (H7N9) virus occurred in Shaanxi, China, in May 2017. Genomic samples studied from human and live poultry markets of farms indicate that H7N9 is spreading westward from Southern and Eastern China.

As expert said; "the world is always worried about avian flu outbreaks." Avian influenza (AI): Is caused by the highly pathogenic avian influenza (HPAI) type A H5N1 virus subtype. AI type A viruses usually do not infect humans; rare human cases have been reported, with most infections occurring after direct or close contact with infected poultry or eating raw or undercooked poultry meat, eggs, or blood from infected birds.

The map (Fig. 19.5) shows the geographic distribution of the total number of highly pathogenic avian influenza A (H5N1 and H5N6) and low pathogenic A (H7N9 and H9N2) virus cases and deaths until of November 2016.

- HPAI type A H5N1 virus is an unusually aggressive virus (rapid deterioration, 60% mortality) that first infected humans in 1997 during a poultry outbreak in Hong Kong, China
- Since November 2003, more than 600 sporadic cases of human HPAI A H5N1 virus infection have been reported, primarily in 15 countries in Asia, Africa, the Pacific, Europe and the near East
- On January 8, 2014, the first reported human case of HPAI A H5N1 virus infection was reported in the Americas (Canada)
- The *low pathogenic A H7N9 virus subtype tends to affect people with underlying comorbidities*; it first infected 3 people in China in March 2013 (2 in Shanghai; 1 in Anhui province), but no cases of A H7N9 infection outside of China have been reported
- Strongly consider the diagnosis of avian influenza (AI) in travelers from endemic regions
- The IP for A H5N1 is 2–8 days (possibly ≤17 days); that for A H7N9 is also 2–8 days (average, 5 days)
- Clinical features depend on which A virus caused the infection. Low pathogenic AI A virus infections are generally mild, nonfatal illnesses; sign and symptoms (s/s) range from conjunctivitis to ILI to pneumonia that requires hospitalization
- HPAI infections range from mild illness to severe respiratory illness and multiorgan disease, sometimes

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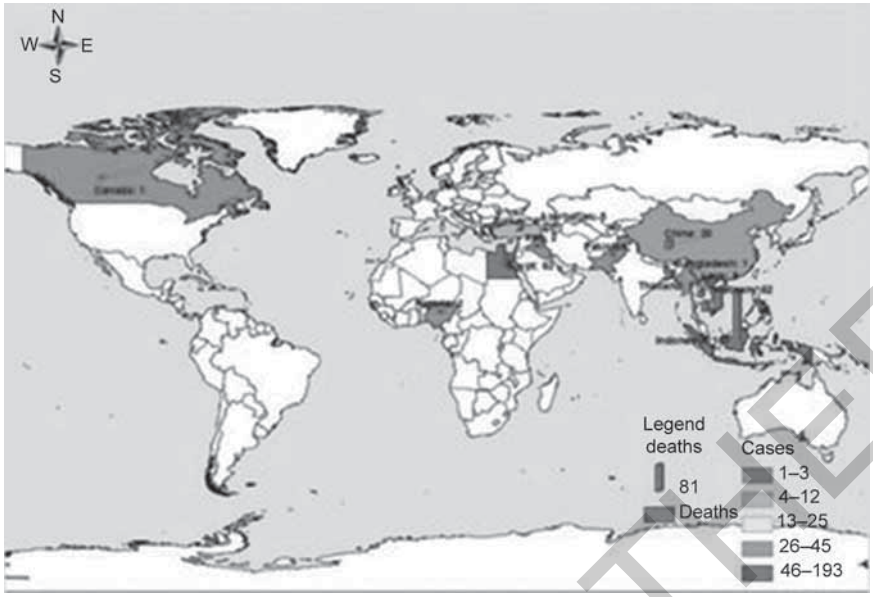

Fig. 19.5: Geographic distribution of avian influenza A virus.
(*Courtesy*: CDC and Redbook 2018)

accompanied by nausea or vomiting, diarrhea, abdominal pain and neurologic changes

- Complications of A H5N1 and A H7N9 infection include hypoxemia, multiorgan dysfunction and secondary bacterial and fungal infections. AI disease can be fatal; these strains with presence of mammalian adaptation markers have pandemic potential
- The diagnosis usually requires laboratory testing (molecular, culture, or both) on nasopharyngeal swabs collected from affected patients during the first few days of illness (*see* Table 19.4)
- The CDC and WHO recommend oseltamivir or zanamivir, two of the four prescription antiviral medications licensed for use in the United States, for treatment and prevention of human infection with AI A viruses
- The best way to prevent infection with AI, A viruses is to avoid sources of exposure. To reduce the risk of exposure to AI and other foodborne diseases when traveling to an area that has an outbreak, avoid visiting live-bird markets, wear protective clothing and special breathing masks when working with birds and avoid undercooked or uncooked meat
- Seasonal influenza vaccination will not prevent infection with AI A viruses, but it can reduce the risk of coinfection with human and AI A viruses
- Ongoing field trials on a candidate live attenuated (LAIV) H7N9 vaccine was well tolerated, safe and showing good immunogenicity. However, annual seasonal—specific influenza vaccines remain the main defense.

Diagnosis

- Nasopharyngeal secretions obtained by swab, aspirate, or wash for "rapid diagnostic flu tests" usually provide results within 15 minutes, although their reported sensitivity (44–97%) and specificity (76–100%) compared with viral culture.

There are many rapid diagnostic tests are in the market. Some rapid flu tests can help distinguish between influenza A and influenza B virus. As with any tests, the accuracy of the test depends on the quality of the manufacturer's test, sample collection method and how much viral sample a person is shedding at the time of testing.

The new FilmArray respiratory panel tests are available to maximize viral specific diagnosis by identifying the accurate cause of respiratory tract viral infections and identify a wide range of 14 respiratory pathogens—not just flu A and flu B.

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Different aspects of infectious disease are addressed and each chapter begins with an annotation of key terms, and definitions and finishes with a concrete summary, using bullet points. The excellent tables and illustrative figures in each chapter are presented with useful proactive diagnostic essentials including nonculture-based molecular advances for early diagnosis and appropriate management. Thirty different chapters are dealt from subject matters on antibiotic uses, vaccine prevention strategies for all ages, and disease transmission control in hospital care environments.

MI Sahadulla MD FRCP (Ire) FRCP (Lon) MBA A luminary in Internal Medicine, Dr MI Sahadulla is the Chairman and Managing Director of KIMS Healthcare Group. He had earlier worked with Saudi Aramco Hospitals for three decades where he was involved in Healthcare Quality, Infection Control and Accreditation and subsequently as Healthcare Manager. He has received many national and international awards including the ACHSI Gold Medallion Award (2015), the first Asian to win this award. His vast experience in the field of quality healthcare delivery makes him a champion in healthcare in India.

Sayenna A Uduman MD FAAP is a graduate of Madras University and obtained his pediatrics training at the Children Hospital Medical Center in Boston. He further specialized in Infectious Diseases and Research Clinical Virology at the New York School of Medicine and Bellevue Hospital. In over 4 decades, he has garnered clinical and research expertise in large quaternary academic institutions, worldwide. He has authored over 100 publications and abstracts. Additionally, he is a globally well acknowledged medical educator. His scholarly area of expertise is in invasive bacterial and viral diseases, vaccinology and antibiotic stewardship programs. Regular participant and meeting attendee of the Advisory Committee on Immunization Practices (CDC).

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