PLAGUE

Causative Agent
*Yersinia pestis*

Incubation Period
2-6 days

Infectious Period
Throughout duration of illness (pneumonic plague is the most important infectious form).

Transmission
Transmitted from rats by flea bites, by handling infected animal tissues, or airborne by aerosol from animals or humans with pneumonic plague.

Epidemiology
There are natural foci of plague infection of rodents in many parts of the world. Wild rodent plague is present in central, eastern and southern Africa, South America, the western part of North America and in large areas of Asia. In some areas, contact between wild and domestic rats is common, resulting in sporadic cases of human plague and occasional outbreaks.

In Southeast Asia, Myanmar and Vietnam report the highest number of cases.

Clinical Features
Plague should be suspected in anyone with fever and painful lymphadenopathy who has been to an endemic country.

There are three principal clinical presentations:

- **Bubonic plague**: initial fever, headache, myalgia followed by painful acute regional lymphadenopathy (pathognomonic bubo), typically involving the inguinal, axillary or cervical regions. If left untreated, rapid progression to septicaemia and secondary plague pneumonia occurs (fatality 50 - 60%).

- **Septicaemic plague**: occurs when *Y. pestis* invades the bloodstream. It can follow bubonic plague or occurs without detectable lymphadenopathy (primary septicaemic plague). Complications include septic shock, disseminated intravascular coagulation, meningitis and multiorgan failure.

- **Pneumonic plague**: the least common but the most dangerous and fatal form of the disease. It can develop as a complication of septicaemic plague or be acquired directly by inhalation of aerosols from a human or animal with pneumonic plague. The signs include severe pneumonia, fever, dyspnoea and
often haemoptysis. Patients who do not receive treatment within 18 hours of onset of respiratory symptoms are unlikely to survive.

**Investigations**
- Blood, bubo aspirate, sputum/throat swab, necropsy material can be sent for isolation of *Y. pestis*.
- Acute and convalescent serology for fourfold rise in titre. A single titre >1:16 is suggestive.
- Inform the laboratory beforehand so that arrangements can be made to forward samples if necessary to the Department of Pathology, Singapore General Hospital, or other designated sites.

**Notification**
A legally notifiable disease in Singapore. Notify Ministry of Health (Form MD 131 or electronically via CD-LENS) not later than 24 hours from the time of diagnosis. Call MOH Communicable Diseases Surveillance team at: 98171463 immediately on suspicion.

**Management**
All cases must be managed at the Communicable Disease Centre (CDC).

Gentamicin, streptomycin, chloramphenicol or tetracycline are highly effective if used within hours of presentation.

**Infection Control**
- Patients with uncomplicated infection who are promptly treated present no health hazard to others.
- Those with cough and other signs of pneumonia must be placed in strict respiratory isolation for at least 48 hours after the institution of antibiotic therapy or until the sputum culture is negative.
- Bubo aspirate and blood must be handled with gloves and aerosolization of these materials should be avoided.
- Laboratory workers must be alerted to exercise precautions although standard bacteriological techniques that safeguard against skin contact and aerosolization should be adequate.

**Prevention and Control**
- All cases will be isolated at CDC, Tan Tock Seng Hospital.
- Case investigations will be carried out and contact tracing will be intensified.
- In the event of death, proper disposal of the body is important.
- Cases and close contacts, including their clothing and personal belongings, will be disinfected with insecticide dusting.
- Anti-flea measures and rodent trapping will be increased at the focus of transmission.
- The public and the World Health Organisation will be informed of all suspected and confirmed cases.
- The public will be advised to step up measures to prevent rodent infestation in the premises and to avoid contact with rodents (either live or dead).

**Chemoprophylaxis**
Consider antibiotic prophylaxis for the following:
- Persons exposed to patients with pneumonic plague.
- Persons exposed to bites of wild rodent fleas during an outbreak or to tissues/fluids of a plague-infected animal.
- Persons travelling to highly endemic area for short duration.

For adults, doxycycline is the best choice (100mg orally bd for 7 days). Trimethoprim-sulfamethoxazole is a suitable alternative.

**Indications for vaccine usage**
A formalin-killed plague vaccine has been used for the following groups:
- Travellers to endemic or hyperendemic areas.
- Individuals who must live and work in close contact with rodents.
- Laboratory workers who must handle live cultures of *Y. pestis*.
- Military personnel deployed in plague-endemic areas.

This vaccine is not routinely available in Singapore.

**References**
PNEUMOCOCCAL DISEASE (INVASIVE)

Causative agent
*Streptococcus pneumoniae* (also known as pneumococcus)

Incubation Period
Not well defined as colonization usually precedes invasive disease; may be as short as 1 to 3 days.

Infectious Period
Presumably as long as pneumococci are carried in oro-nasal secretions in asymptomatic individuals (colonization usually lasts weeks to months); with penicillin treatment, persons infected with susceptible strains are rendered non-infectious within 24-48 hours.

Transmission
Respiratory droplets and direct contact with respiratory secretions of an infected person (usually requires frequent or prolonged close contact).

Epidemiology
*S. pneumoniae* is one of the most common causes of invasive infections such as bacteremia, meningitis and bacteraemic pneumonia, and bacterial mucosal infections such as sinusitis and otitis media. Of the 91 pneumococcal serotypes, 23 account for the vast majority of invasive pneumococcal disease (IPD) in humans. The worldwide emergence of pneumococcal resistance to antibiotics, including beta-lactams, macrolides, tetracycline, cotrimoxazole and fluoroquinolones has been a considerable concern.

Invasive pneumococcal infection is defined as the isolation of *S. pneumoniae* from normally sterile sites such as blood, pleural fluid and cerebrospinal fluid (CSF). Pneumococcal pneumonia is considered an invasive disease but would be excluded if blood or pleural fluid cultures are sterile. Otitis media is not considered an invasive disease, but may be included if *S. pneumoniae* is isolated from normally sterile middle ear fluid.

In Singapore, the mean annual hospitalisation rate for IPD from 2000-2008 was 8.9 per 100,000 population (about 380 cases per year). A total of 157 deaths from IPD were reported during this period, of which 5 were under the age of 5 years. In 2009, there were 251 reported cases of IPD. Of these, 124 met the criteria for IPD. The highest incidence rate was in children <5 years of age and the elderly aged 65 years and above. In children, serotypes 14, 6B, 23F, 19F, 6A and 19A were the most common strains isolated, and accounted for 89% of all invasive diseases in children <5 years old. However, in adults, isolate distribution was more spread out and
common ones were 14, 3, 6B, 8 and 19F which accounted for 51% of all invasive diseases. Mean case fatality rates for IPD in single-centre series were 6.1% in children but rising to 30% in children with pneumococcal meningitis; while in adults, this was 21.4%.

A pneumococcal polysaccharide vaccine (23-valent or serotype) has been available locally since 1988. It was recommended for children >2 years old with risk factors for IPD and adults >65 years old, but its immunogenicity was fair and its uptake was very poor. However, it would cover 82.8% of IPD serotypes in adults. A highly immunogenic pneumococcal conjugate vaccine (7-valent) was licensed locally for children 6 weeks to 9 years old since 2002 but became commercially available locally only since late 2005, with uptake primarily in children <5 years within the private sector. In November 2009, it became the 10th vaccine-preventable disease to be included in the National Childhood Immunization Programme.

Clinical Features

- Typically between 40-50% of children and 20-30% of adults carry pneumococci asymptomatically in their nasopharynx.
- Infection is often preceded by a respiratory viral illness before local disease (from congestion and concentration of virulent pneumococci) or invasion leading to systemic or invasive disease
- Can infect any organ.
- Mucosal infections include acute otitis media, bacterial sinusitis, conjunctivitis.
  - Otitis media may be complicated by mastoiditis and intracranial extension with abscess formation.
  - Sinusitis may be complicated by periorbital or orbital cellulitis, with resultant intracranial extension.
- Common deep-seated or invasive infections include primary bacteraemia, pneumonia (with or without bacteraemia; pneumonia without bacteraemia is not traditionally classified as “invasive”), and meningitis.
  - Pneumonias may be complicated by parapneumonic effusions and empyemas.
  - Meningitis is infrequently associated with development of subdural empyemas, intracranial abscesses and vasculitic/thrombotic phenomena.
- Less commonly, it can also cause osteomyelitis, pyogenic arthritis, endocarditis, myocarditis, pericarditis, bacterial peritonitis, endophthalmitis and salpingitis.
- In some patients (especially those who are immunocompromised), pneumococcal infections may be fulminant and present with overwhelming sepsis and multi-organ failure.
Risk Factors:
- Age (<5 years and >65 years)
- Racial predisposition (though not evident in local series)
- Chronic illnesses (chronic respiratory, heart, renal and liver disease, alcoholism, diabetes)
- Cochlear implants
- Cerebrospinal fluid leaks
- Functional or anatomic asplenia/ splenic dysfunction (including sickle cell disease)
- Immunocompromised—either congenital, acquired (e.g. HIV infection) or iatrogenic via immunosuppression.

Investigations
- Microbiological confirmation by culture remains the gold standard for diagnosis and allows for sensitivity testing as well as subsequent serotyping; however the yield in blood may be low for different pneumococcal syndromes—high in meningitis, low (around 25%) in pneumonia.
  - The volume of inoculum (usually blood, uncommonly pleural fluid or CSF) is important, and blood cultures (if positive) are usually positive within 18 hours of inoculation
- Gram stains and latex agglutination testing of infected body fluids (e.g. CSF, pleural, peritoneal or joint fluid) should always be performed and may be helpful, although other streptococci may also appear as Gram-positive diplococci and latex agglutination testing lacks sensitivity.
- Urinary pneumococcal cell wall polysaccharide (antigen) testing is currently available and a positive result is strongly suggestive of pneumococcal disease/ pneumonia in adults, although it can be positive in the setting of acute nasopharyngeal carriage (as often occurs in children) and hence the specificity is much poorer in children.
- Imaging (e.g. X-ray, computerised tomography, ultrasound, and nuclear or magnetic resonance imaging) assists in localising infection in patients with appropriate clinical symptoms and signs

Notification
A legally notifiable disease in Singapore. Notify Ministry of Health (Form MD 131 or electronically via CD-LENS) not later than 72 hours from the time of diagnosis.

Management
- Appropriate resuscitation, oxygenation and invasive or supportive care as required; the importance of this cannot be overemphasized.
Initial choice of empirical antibiotics should be guided by local age-appropriate guidelines for respective clinical syndromes (by institution or college).

Once confirmed microbiologically, appropriate, targeted antibiotic treatment should be guided by susceptibility testing after the initial empirical regime.

- Penicillins (followed by 1st and 2nd generation cephalosporins) are the preferred choice of antimicrobials; however, depending on the site of infection, much higher doses may be required, or 3rd generation cephalosporins may be used (e.g. meningitis).
- Where pneumococci are resistant to beta-lactams, treatment may be individualized with vancomycin, quinolones or tetracyclines as appropriate.

Source control (e.g. drainage of infections in closed spaces like empyemas or cerebral abscesses) are often critical to success or failure of antibiotic treatment.

Adjunct therapies may also need to be considered e.g. dexamethasone in pneumococcal meningitis, activated protein C in severe pneumococcal sepsis.

Prevention and Control

- All children <2 years old should receive pneumococcal conjugate vaccine as recommended under the National Childhood Immunization Program.
  - Children <1 year old should receive 2 primary doses at 3 months and 5 months followed by a booster at 1-2 years.
  - Children >1 year old should receive age appropriate doses of pneumococcal conjugate vaccine and also depending on whether they have risk factors for IPD.
- All adults ≥65 years old, and persons 2 to 64 years with risk factors for IPD (as above) should receive 23-valent pneumococcal polysaccharide vaccine as recommended by MOH.
- All childhood vaccinations should be notified to the National Immunisation Registry, Health Promotion Board. All post vaccination adverse reactions should also be notified to the Pharmacovigilance Branch, Health Sciences Authority.
References

POLIOMYELITIS

Causative Agent
Poliovirus, types 1, 2 and 3

Incubation Period
7-14 days (Range 5-35 days)

Infectious Period
A few days before and after onset of illness.

Transmission
Faeco-oral or respiratory transmission.

Epidemiology
The last indigenous case of poliomyelitis notified in Singapore was in 1973.

Globally, polio cases have decreased by over 99% since 1988, from estimated 350,000 cases then to 1997 reported cases in 2006. In 2008, only four countries remain endemic (northern India, northern Nigeria and border between Afghanistan and Pakistan).

Clinical Features
- Disease manifestation can range from subclinical infection to severe paralysis and death.
- The infection should be suspected in someone with a history of an incomplete immunisation against polio or recent travel to an endemic country.
- Three forms of paralytic polio may be seen:
  1. Spinal Paralytic Polio
     This is preceded by a “minor” illness with fever, muscle pain, headache, nausea, vomiting and stiff neck/back and less frequently, signs of aseptic meningitis. The minor illness lasts 1-3 days followed by a symptom-free period of 1-5 days before the onset of “major” illness of paralysis. Paralysis which varies from single muscle involvement to quadriplegia, is usually asymmetric and typically flaccid with loss of tendon reflexes. There is no accompanying sensory loss.
  2. Bulbar Paralytic Polio
     Paralysis of the soft palate, pharynx and larynx resulting in dysphagia, nasal speech and dyspnoea.
  3. Polioencephalitis
     Encephalitis is manifested by confusion and change in sensorium. This is an uncommon form of polio seen in infants. Seizures are common and there may be spastic paralysis as opposed to flaccid paralysis.
The most common differential diagnoses are those causing acute flaccid paralysis including transverse myelitis, Guillain-Barré Syndrome, enterovirus 71 and West Nile virus infections.

Investigations
- CSF findings consistent with any viral meningitis. CSF protein is minimally elevated (unlike in Guillain-Barre syndrome).
- Polioviruses can usually be isolated from the throat swab in the first week of illness and stool cultures may remain positive for several weeks.
- In the absence of a virus isolate, the diagnosis is confirmed by a four-fold increase in antibody titre of the acute and convalescent sera.

Notification
A legally notifiable disease in Singapore. Notify Ministry of Health (Form MD 131 or electronically via CD-LENS) not later than 72 hours from the time of diagnosis.

Management
Refer all confirmed cases to the Communicable Disease Centre (CDC), Tan Tock Seng Hospital, for isolation and management. Specific anti-viral therapy is not available. Management is therefore supportive and symptomatic.

Prevention and Control
- Case investigation and contact tracing will be carried out to identify unrecognised and unreported cases. Contacts below 12 years old without complete immunisation will be referred to the nearest Polyclinic or School Health Clinic for vaccination.
- All infants are routinely vaccinated against poliomyelitis as part of the Childhood Immunisation Programme in Singapore.
- Both IPV (inactivated polio vaccine) and OPV (live, attenuated vaccine) have been used for more than 30 years in controlling paralytic poliomyelitis. IPV should be used for immunocompromised children and adults including travellers.
- Notify all childhood vaccinations to the National Immunisation Registry, Health Promotion Board, and post-vaccination adverse reactions to the Pharmacovigilance Branch, Health Sciences Authority.

References
RABIES

Causative Agent
Rabies virus

Incubation Period
20 - 90 days (range 4 days - 19 years)

Infectious Period
Throughout duration of clinical illness

Transmission
From saliva of infected animals via bites. Rarely, contamination of mucous membranes by infectious material, aerosol transmission and organ transplantation.

Epidemiology
Although reservoir is present in many mammalian species, dog bites account for the majority of human infections. Rabies has not been reported locally since 1953. but remains prevalent in many parts of the region and the world. Recent decrease in human rabies cases has been due to improved post-exposure treatment as well as elimination of rabies in animal reservoirs via oral immunisation of wildlife.

Clinical Features
- The first symptoms of rabies usually begin when the virus enters the CNS. A non-specific prodrome of 2-10 days includes fever, malaise, fatigue, anorexia, cough, sore throat, abdominal pain, nausea, vomiting or diarrhoea. The first rabies-specific symptom is pain or paraesthesia referred to the site of the exposure.
- The acute neurological period manifests as either a hyperactive (furious rabies) in 80% or a paralytic (dumb rabies) form in 20%. Autonomic instability is often prominent (hyperthermia, salivation, hypertension and tachycardia).
- The neurological phase lasts 2-7 days before development of coma then death.

Investigations
No tests are available to diagnose human rabies during the incubation period.

After onset of clinical disease, diagnostic methods include:
- Direct fluorescent antibody staining of skin biopsy from nape of neck (50%).
- Rabies neutralising antibodies in serum or CSF.
- Rabies virus isolation from saliva, CSF, urine and tracheal secretions (low).
- Rabies RT-PCR in saliva, CSF, urine and tissue.
- Cortical brain biopsy.
  ▪ Specimens may need to be sent overseas for tests.
Post-mortem brain examination for Negri bodies and fluorescent staining for rabies antibodies.

Notification
Notify all suspected and confirmed cases immediately. Call MOH Communicable Diseases Surveillance team at 98171463 and the Agri-Food and Veterinary Authority of Singapore (AVA) for further investigation.

Management
- There is no specific treatment for clinical human rabies. Intensive supportive care in the ICU is often used although mortality is virtually 100%.
- Standard and respiratory precautions should be observed by healthcare workers caring for such patients. Pre-exposure immunisation of medical staff is generally not required. Routine delivery of healthcare is not an indication of post-exposure prophylaxis unless the healthcare worker is reasonably certain that he or she was bitten or mucous membranes or non-intact skin was exposed to potentially infectious saliva or neural tissue.

Prevention and Control
- In rabies-free Singapore, the AVA exercises strict control on importation and quarantine of dogs, cats and wild animals and intensive control of stray dog and cat population.
- In the case of human exposure to animals suspected of having rabies, immediate attempts should be made to identify, capture or kill the animal involved. The veterinarian, AVA, will remove the brain of the animal to examine for presence of rabies virus antigen by immunofluorescence.

Pre-Exposure Vaccination
- For travellers visiting rabies endemic countries (Central and South America, Africa, Indian subcontinent and Southeast Asia), pre-exposure vaccination may be recommended depending on intended activity, duration of stay, local incidence of rabies and availability of appropriate anti-rabies biologicals.
- Pre-exposure vaccination greatly simplifies but does not eliminate the need for post-exposure treatment.
- Pre-exposure vaccination consists of 3 doses given on days 0, 7 and 21 or 28 days.
- The human diploid cell vaccine (HDCV) is an inactivated virus vaccine available in Singapore.

Post-Exposure Treatment
- The most effective mechanism of protection against rabies is to wash and flush a wound or point of contact with soap and water, followed by application of ethanol, tincture or aqueous solution of iodine.
- Suturing should be postponed and where indicated, anti-tetanus toxoid and antimicrobials should be administered.
- Rabies vaccine and immunoglobulin should be given as soon as possible if indicated (see table below). Post-exposure vaccination consists of 5 doses given on days 0, 3, 7, 14 and 28. Tan Tock Seng Hospital, keeps a stock of rabies vaccine and human rabies immunoglobulin.

**Guide for Post-Exposure Treatment**

<table>
<thead>
<tr>
<th>Category</th>
<th>Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for observation</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Touching or feeding of animals. Licks on intact skin.</td>
<td>None, if reliable case history is available.</td>
</tr>
<tr>
<td>II</td>
<td>Nibbling of uncovered skin. Minor scratches or abrasion without bleeding. Licks on broken skin.</td>
<td>Administer vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or if animal is euthanised and found to be negative for rabies by appropriate laboratory techniques.</td>
</tr>
<tr>
<td>III</td>
<td>Single or multiple transdermal bites or scratches. Contamination of mucous membrane with saliva (i.e. licks).</td>
<td>Administer rabies immunoglobulin and vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or if the animal is euthanised and found to be negative for rabies by appropriate laboratory techniques.</td>
</tr>
</tbody>
</table>


b If an apparently healthy dog or cat in or from a low-risk area is placed under observation, it may be justified to delay specific treatment.

c This observation period applies only to dogs and cats. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be euthanised and their tissues examined using appropriate laboratory techniques.
References

RUBELLA

Causative Agent
Rubella virus

Incubation Period
2 - 3 weeks

Infectious Period
Few days before until seven days after onset of rash. Infants with congenital rubella syndrome may shed the virus from their body secretions for 1 year or more after birth.

Transmission
Respiratory droplets and direct contact with nasopharyngeal secretions.

Epidemiology
Rubella immunisation was introduced in Nov 1976 for female primary school leavers at 11+ years of age. However as rubella outbreaks continued to occur in susceptible populations especially national servicemen (NS men), the vaccination was extended to cover male primary school leavers in 1982. NS men were also routinely vaccinated to eliminate rubella in army camps. The programme was further expanded to include children 1-2 years of age using the trivalent measles, mumps, rubella (MMR) vaccine in Jan 1990. The 2nd dose of MMR was introduced in 1997 for secondary and junior college students in a catch-up measles vaccination programme and to all primary school leavers in 1998. Since 2008, the 2nd dose of MMR vaccine is now given at 6-7 years of age (primary 1) under the revised National Childhood Immunisation Programme.

The rubella incidence peaked in 1996 with 487 notifications. With the catch-up measles vaccination program, the number of rubella cases has gradually declined from 10.9 cases per 100,000 population in 1999 to 3.6 per 100,000 in 2009. The incidence of congenital rubella is about 0-2 cases per year since 1995.

In a serosurveillance study of rubella conducted in 1998, it was found that the overall immunity of the population to rubella was 80.2% with the lowest immunity in the 10-14 year age group (65.5%). Another survey in 2004 showed that 15.8% of women aged 18 to 44 years were non-immune to rubella (a relatively high level compared to women of reproductive age in other developed countries).

It is important to ensure that at least 95% of the children are immunised at 1-2 years of age. Congenital rubella can only be completely eliminated if every woman in the
15-44 year age group is immunised against the disease. Women should be advised to be vaccinated before they are married and prior to conception.

**Clinical Features**

- Many cases are subclinical.
- Infection usually starts with a mild prodrome and appearance of tender occipital, post-auricular and cervical lymphadenopathy which precedes the appearance of the rash.
- Prodromal symptoms include low grade fever, headache, malaise, anorexia, mild conjunctivitis, coryza, sore throat, cough and lymphadenopathy. The symptoms last 1 - 5 days and subside rapidly after the rash appears.
- An enanthem consisting of reddish spots on the soft palate may be observed in the prodromal period or on the first day of the rash but is not diagnostic.
- The rash progresses in a cephalo-caudal direction and usually subsides in 3 days. By the end of the first day, the body is covered with red, discrete maculopapules. By the third day, the rash disappears without any staining or desquamation.
- The spleen may be slightly enlarged.
- Fever if present is usually low grade and lasts 1 - 3 days.
- Complications such as arthralgia and arthritis, which are more common in adults, clear in about 5 - 10 days. Encephalitis and thrombocytopaenia are rare complications.
- The risk of foetal infection and congenital anomalies depends on stage of pregnancy at which infection occurs (lower risk after 20 weeks).

**Differential diagnoses include:**

- Exanthem subitum (Roseola infantum)
- Drug rash
- Infectious mononucleosis
- Enteroviral infections
- Mild measles
- Scarlet fever

**Investigations**

- Indicate on the request form a brief clinical history, as the assays used for immunity screening and for diagnosing recent infection may differ.
- Rubella can be diagnosed by demonstrating a fourfold rise in IgG antibody titres between acute and convalescent samples and by detecting rubella-specific IgM antibody.
- Rubella-specific IgM antibody is usually detectable by five days after onset of illness and remains detectable for at least one month but commonly for two months.
Caution is advised in interpretation of rubella IgM antibody tests since false positive results are not uncommon. They may arise during other virus infections such as those due to parvovirus B19, CMV or EBV.

**Notification**

A legally notifiable disease in Singapore. Notify Ministry of Health (Form MD 131 or electronically via CD-LENS) not later than 72 hours from the time of diagnosis.

**Management**

- Patient is managed symptomatically.
- If infection occurs in early pregnancy, the patient should be referred to a gynaecologist or an infectious disease physician who can provide advice and counselling on the possible risks of congenital malformation and appropriate management at that point in pregnancy.
- Patients should be isolated from non-immune persons (with droplet precautions) for seven days after onset of rash.

**Prevention and Control**

- Combined measles/mumps/rubella (MMR) vaccine is given to all pre-school children at the age 12-15 months and primary school entrants at the age of 6-7 years as part of the National Childhood Immunisation Programme (see Appendix 2).
- Rubella vaccination is also routinely offered at polyclinics to non-immune married women and mothers who have just delivered their first babies.
- All unimmunised children at nurseries, kindergartens and schools where an outbreak is occurring should be immunised.
- The vaccine should be avoided in pregnancy and women who received rubella vaccine should be advised to avoid pregnancy for one month after vaccination. The observed risk for vaccine-associated congenital rubella is zero but the theoretical risk is as high as 2%. The currently recognised theoretical risk does not mandate automatic termination of pregnancy if a woman has been inadvertantly vaccinated with rubella vaccine.
- All childhood immunisations should be notified to the National Immunisation Registry, Health Promotion Board. Post-vaccination adverse reactions should also be notified to the Pharmacovigilance Branch, Health Sciences Authority.

**References**

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

Causative Agent
SARS-associated coronavirus (SARS-CoV)

Incubation Period
Typically 2-7 days but may be prolonged up to 10-14 days

Infectious Period
Throughout the symptomatic phase of the disease.

Although there may be persistent viral shedding in the stool for up to 6 weeks after recovery from clinical illness, transmission of the disease has not been documented from asymptomatic nor convalescent individuals.

Transmission
Respiratory droplets and less often by direct contact with objects contaminated by respiratory secretions. Oral-faecal and airborne transmission may occur under special circumstances.

Epidemiology
The first outbreak of this new infectious disease occurred in Guangdong, China in November 2002, but soon spread to several Asian countries and Canada by March 2003. The outbreak ended on 5th July 2003, although two cases attributed to laboratory transmission were reported from Singapore and Taiwan in September and December 2003, respectively. Another laboratory associated outbreak occurred in China in April 2004.

The majority of transmission occurred in hospitals and other institutional healthcare settings.

By the end of the worldwide outbreak in July 2003, a total of 8096 cases were reported, with 774 deaths and a case-fatality rate of 9.6 percent.

Between March and May 2003, a total of 238 cases, with 33 deaths, were reported in Singapore. 41% of the cases were healthcare workers, and 68% were females. The median age of all SARS cases was 36 (range 4 to 90) years.
Clinical Features

- The clinical presentation is non-specific and resembles other influenza-like illnesses.
- The prodrome is prolonged lasting from 3 to 7 days and is characterised by fever, malaise, headache and myalgia. Respiratory symptoms and diarrhoea, if present, typically occur a few days after the onset of fever.
- Physical examination is not helpful except as a gauge of severity of illness.
- Clinical manifestations vary from mild infection (80%) to severe disease (20%) with respiratory failure and death.
- Death is usually caused by combination of respiratory and multiorgan failure.
- The clinical course is marked by deterioration in the second week of illness and recovery by the third week in the majority of cases. Children have a shorter and milder course of illness.
- There is no evidence at present of intra-partum infection.

Investigations

- Chest X-ray. This may be normal early in the course of the disease. However, the more distinct radiographic features include:
  - a predominantly peripheral location of air-space opacity;
  - progression from unifocal to multifocal or bilateral lung involvement during treatment; and
  - lack of cavitation, lymphadenopathy and pleural effusion.

Case Definitions

- At the time of and in the immediate aftermath of the SARS epidemic, both the World Health Organization (WHO) and the US CDC issued case definitions for SARS.
- According to the WHO, a case of SARS is notifiable if it occurs in an individual with laboratory confirmation of infection who either meets the clinical case definition or has worked in a laboratory with live SARS coronavirus or with clinical specimens infected with SARS coronavirus.
- The clinical case definition used by the WHO includes:
  - A history of fever or documented fever; and
  - One or more symptoms of lower respiratory tract illness (cough, difficulty in breathing, shortness of breath); and
  - Radiographic evidence of lung infiltrates consistent with pneumonia or acute respiratory distress syndrome (ARDS) or autopsy findings consistent with the pathology of pneumonia or ARDS without an identifiable cause; and
  - No alternative diagnosis fully explaining the illness.
- Laboratory diagnostic tests that are required include one or both of the following:
Detection of virus (reverse transcriptase PCR) assay detecting viral RNA present in two separate samples, or virus culture from any clinical specimen. These two samples can be obtained from either two separate sites (e.g. nasopharyngeal and stool) or from the same site, but at different times (e.g. sequential nasopharyngeal aspirates); and/or

Detection of antibody (a rise in antibody titre, either from negative to positive or at least a four-fold increase) by enzyme-linked immunosorbent assay (ELISA) and/or immunofluorescent assay (IFA).

These are highly sensitive and specific but positive only from the second week of illness onwards.

Notification
A legally notifiable disease in Singapore. Notify Ministry of Health (Form MD 131 or electronically via CD-LENS) not later than 24 hours from the time of diagnosis. Notify MOH immediately on suspicion. Call MOH Communicable Diseases Surveillance team at: 98171463

Management
- All suspected and probable/confirmed cases of SARS will be isolated and treated at the Communicable Disease Centre (CDC).
- Symptomatic and supportive treatment for all cases.
- Ribavirin which was used initially during the pandemic has been shown to be ineffective in vitro towards SARS coronavirus and is associated with significant toxicities.
- Some centres recommend a short course of moderate to high dose corticosteroids.
- There may be a role for treatment using protease inhibitor like lopinavir, immunoglobulins and interferon based on prior experience.

Infection Control
- Patients with SARS should ideally be nursed in negative pressure isolation rooms.
- Respiratory (droplet and airborne) and contact precautions are required.
- Procedures which may aerosolize the virus (viz. nebulizer therapy) should be avoided if possible.
- Movement of patients (viz. for scans or other procedures) within the hospital should be kept to a minimum.

Prevention and Control
- Public health measures to limit transmission include:
  - Shortening the time from symptom-onset to isolation of patients (viz. early case detection)
  - Effective contact tracing
- Quarantine of exposed persons
- Surveillance of fever clusters and atypical pneumonia cases

A combination of clinical and relevant epidemiological features should raise suspicions of SARS. However, it is quite likely that a de novo case will be missed initially, and success of current preventive policies will be gauged by the size of the consequent outbreak.

Efforts are underway to prepare a vaccine but are still at an early stage.

References
8. Case definitions for the 4 diseases requiring notification to WHO in all circumstances under the IHR (2005). Wkly Epidemiol Rec 2009; 84:52
SEXUALLY-TRANSMITTED INFECTIONS

Causative Agents
In 2009, the top 5 sexually-transmitted infections (STIs) diagnosed in Singapore were: *Chlamydia trachomatis* (infection of the urethra, cervix, pharynx and rectum), *Neisseria gonorrhoeae* (infection of the urethra, cervix, pharynx and rectum), non-gonococcal urethritis (NGU), herpes simplex virus (HSV): types 1 and 2 (ano-genital herpes), and human papilloma virus (HPV) (ano-genital warts). Other important STIs are *Treponema pallidum* (syphilis), *Trichomonas vaginalis* (trichomoniasis), and human immunodeficiency virus infection (HIV).

Incubation Period
Chlamydia : 5 - 14 days
Gonorrhoea : 3 - 5 days
Ano-genital herpes : 2 - 14 days
Ano-genital warts : 1- 6 months (mean 3 months)
Syphilis : 10 - 90 days (mean 21 days)
Trichomoniasis : a few days
HIV : mean of 1 month to acute HIV infection, mean of 5 to 8 years to AIDS if untreated

Infectious Period
Gonorrhoea, chlamydia : active infection, symptomatic or asymptomatic
Ano-genital herpes : presence of vesicles and erosions; asymptomatic viral shedding is also an important route of transmission
Ano-genital warts : higher with presence of active lesions; subclinical infections common
Syphilis : during primary and secondary stages
Trichomoniasis : active infection, symptomatic or asymptomatic
HIV infection : infectious from early on till demise if untreated

Clinical Features
STI may present with:
- genital discharges (gonorrhoea, chlamydia, trichomoniasis)
- ano-genital ulcers (herpes, syphilis)
- ano-genital growths (warts, molluscum contagiosum)
- rashes (syphilis, scabies)
- pelvic inflammatory disease (gonorrhoea, chlamydia)
- epididymo-orchitis (gonorrhoea, chlamydia)
- HIV infection may present in several ways depending on the organ systems affected (see chapter on HIV).
Many STIs may be asymptomatic and can be detected only if the appropriate laboratory screening tests are performed (see references).

**Investigations and Guide to Diagnosis**

- **Ano-genital Herpes (First episode/ Recurrent)**
  - Typical vesicles or erosions in the ano-genital area (may be severe with initial episode).
  - Confirmed by viral isolation, direct immunofluorescence (DIF), PCR, EIA or type-specific serological test against glycoprotein gG1 (HSV-1) & gG2 (HSV-2) for HSV (serology is not useful for first episode infection as it takes between 6 and 8 weeks for serological detection following a first episode).

- **Chlamydia Genital Infection—(A laboratory diagnosed infectious disease)**
  - Nucleic acid amplification test (NAAT) (e.g. PCR) positive for *C. trachomatis* from ano-genital specimen or urine; or
  - Antigen detection (e.g. EIA, IF) positive for *C. trachomatis* from ano-genital specimen.
  - Chlamydia serology is not useful as it does not distinguish between past or current infection; there is also cross-reactivity with other chlamydial species.

- **Gonorrhoea**
  - Purulent genital discharge (associated with dysuria in males), history of recent unprotected sexual intercourse; or
  - Gram-stained smear from genital discharges with Gram-negative intracellular diplococci; or
  - Positive culture on selective media for *N. gonorrhoeae*; or
  - Urine nucleic acid amplification test (NAAT) (e.g. PCR) positive for *N. gonorrhoeae*.
  - Gonorrhoea serology is not useful due to lack of sensitivity & specificity.

- **Non-Gonococcal Urethritis (NGU)**
  - Mucopurulent or whitish discharge from urethra associated with dysuria or urethral discomfort/itch in males, history of recent unprotected sexual intercourse; or
  - Gram-stained smear showing increased pus cell count (5 or more WBC per high-power field) in absence of Gram-negative intracellular diplococci; or
  - Visible threads in the first glass of a 2 glass urine test.

- **Infectious Syphilis**
  - Presence of primary chancre usually solitary, indurated, non-tender (but the ulcer may also be atypical), inguinal lymphadenopathy; or
- Presence of clinical features of secondary syphilis e.g. rash especially on palms and soles, ano-genital patches and growths, generalized lymphadenopathy, patchy hair loss; confirmed by:
  - Positive dark-field microscopic examination of exudate from primary or secondary ano-genital lesions for spirochaetes; or
  - Reactive blood tests for syphilis:
    1. Non-specific treponemal tests (RPR/VDRL)
    2. Specific treponemal tests (TPPA/TPHA, LIA, Syphilis EIA)

Non-Infectious Syphilis
- Presence of clinical features of tertiary syphilis (viz. cardiovascular syphilis, central nervous system syphilis); or
- Asymptomatic infection with reactive blood tests for syphilis
- Note - persistence of reactive serology in patients with treated syphilis may be indicative of a serological scar

Congenital Syphilis
- Presence of clinical features of active disease (e.g. muco-cutaneous signs, bone changes, hepatosplenomegaly) and confirmed by reactive blood tests for syphilis.
- Asymptomatic infection in infant born to infected mother with:
  - Detectable LIA IgM in infant; or
  - RPR/VDRL titre in infant fourfold or greater than in mother; or
  - RPR/VDRL titres show serial rise; or
  - Reactive CSF-VDRL or abnormal CSF FEME in infant.

Trichomoniasis
- Diagnosed by direct wet-mount microscopy and culture. Serology is not useful.

Mycoplasma: There are no clear guidelines for screening with serology.

Candida: Serology is not useful as it is not indicative of a genital cause/disease.

Management
- All patients with a STI should be screened for syphilis, hepatitis B and HIV infection.
- Patients should receive recommended antimicrobials in the correct dosages (see references). Test-of-cure is important to assess treatment efficacy particularly for gonorrhoea and syphilis.
- **Chlamydia:**
  - Doxycycline 100mg bid x 7 days (avoid if pregnant)
  - Erythromycin 500mg qid x 7 days
  - Erythromycin ethylsuccinate 800 mg qid x 7 days
  - Azithromycin 1gm x 1 dose (useful if adherence is an anticipated problem)

- **Gonorrhoea:**
  - All patients with gonorrhoea should be given concurrent treatment for chlamydia.
  - Fluoroquinolones are not recommended due to high prevalence (80%) of resistance in *N. gonorrhoeae*.
  - Repeat smears and cultures should be performed on or around the 14th post-treatment day.
  - For those with penicillin allergy, IM spectinomycin can be used. Or consider allergy testing and desensitization. Specialist consultation recommended.
  - **Uncomplicated** (pharynx/urethra/rectum/cervix):
    - IM Ceftriaxone 250mg x 1 dose; or
    - Cefixime 400mg x 1 dose
  - **Severe or Disseminated Gonococcal Infections (DGI):**
    - IV Ceftriaxone 1-2g daily. Duration depending on site of infection and response

- **Syphilis:**
  - Cases of syphilis should be treated with intramuscular benzathine penicillin. They should have serological tests repeated at 3 months, and then every 6 months for 2 years. Suspected cases of neurosyphilis should have a lumbar puncture performed.
  - For late latent syphilis, syphilis of unknown duration, congenital syphilis, neurosyphilis or syphilis in pregnancy, the treatment recommendations are different and relevant expert advice should be sought.
  - **Primary and Secondary Syphilis:**
    - IM Benzathine Penicillin G 2.4 million units x 1 dose. (Some authorities use 2 doses for secondary syphilis); or
    - IM Aqueous Procaine Penicillin G 600,000 units daily x 10 days
  - Penicillin allergic patients:
    - Doxycycline 100mg bid x 14 days; or
    - Erythromycin 500mg qid x 14 days; or
    - Azithromycin 500mg daily x 10 days
Cases of first-episode genital herpes should be treated with acyclovir or related medications. Recurrent genital herpes may be treated with either episodic or suppressive anti-viral regimens (see references).

Ano-genital warts can be treated medically or surgically; they should be followed up till all visible warts are cleared. Regular PAP smears are recommended for female patients.

Cases of trichomoniasis are treated with metronidazole (see references).

**Notification**

- Chlamydia, gonorrhoea, syphilis (infectious, non-infectious and congenital), NGU, genital herpes (first episode and recurrent) should be notified to the DSC clinic by fax (62994335) using form MD 131 or electronically via CD-LENS.
- Provide information on type of HSV detected where available.
- Repeat notifications of recurrent genital herpes are not necessary.
- The name, NRIC, address and telephone number need **not** be completed, but initials, sex, date of birth, ethnicity and residential status should be provided.

**Prevention and Control**

- Patients with STI should be given information about their current infection.
- To prevent future infections, information on safer sex should be given too e.g. correct and consistent condom use.
- Partner management/contact tracing should be conducted to diagnose and treat infections in sex partners, to prevent complications and further transmission.
- Antenatal mothers should be routinely screened for syphilis, hepatitis B and HIV infection.
- Hepatitis B vaccination should be given to those who are negative for HBV markers.
- Brothel-based sex workers are provided with STI/HIV educational information and taught negotiation skills to achieve 100% condom use; they are screened routinely for syphilis, gonorrhoea, chlamydia, HIV and hepatitis B infections. Targeted STI/HIV education for at risk groups e.g. youth, MSM, military personnel, and clients of sex workers should be conducted regularly.
- Patients are encouraged to seek early treatment, not to self-medicate and to complete all prescribed medications.
- Self-medication with antibiotics may result in the emergence of drug-resistant strains. Medical practitioners should not dispense antibiotic chemoprophylaxis as there is no one universally effective antibiotic, this may also result in a false sense of security and may be dangerous.
References

2. STI Management Guidelines - Department of STI Control, National Skin Centre, 2007
SHIGELLOSIS (BACILLARY DYSENTERY)

Causative Agents
*Shigella sonnei, S. flexneri, S. boydii and S. dysenteriae.*

Incubation Period
Usually 1 - 3 days. Up to 1 week for *S. dysenteriae* type 1

Infectious Period
Throughout duration of acute illness and until the organism is no longer present in the stool, usually within 4 weeks after illness.

Transmission
- Direct or indirect faecal-oral transmission from a symptomatic person or short-term asymptomatic carrier. Also via faecally-contaminated water, milk or food. Transmission by house flies has also been documented.
- As few as 10-100 organisms can cause infection, enabling person-to-person transmission where hygiene conditions are compromised.
- Outbreaks have occurred in homosexual men; under conditions of crowding; and where personal hygiene is poor such as in day care centres, jails, mental institutions and crowded refugee camps.

Epidemiology
Endemic throughout the world with the greatest burden of disease occurring in developing countries afflicting children less than five years of age particularly. *S. sonnei* accounts for the majority of shigellosis in developed countries.

In Singapore, a total of 29 sporadic cases of shigellosis were reported in 2008, as compared to 13 cases in 2007. The serotypes involved were *Shigella sonnei* (75.9%), *Shigella dysenteriae* (13.8%), and *Shigella boydii* (10.3%). Of the reported cases, 17 were local residents comprising 12 indigenous and five imported cases. There were two non-residents that acquired the infection locally. The remaining 10 cases comprised one tourist and nine foreigners seeking medical treatment in Singapore. The five imported cases acquired the infection from Bangladesh (1), Cambodia (1), Hong Kong (1), India (1) and Nepal (1).

Increasing antibiotic resistance to fluoroquinolones (esp. in Asia), nalidixic acid, TMP/SMX, ampicillin and tetracycline, has been reported.

*S. dysenteriae* type 1 (SD1) serotype is responsible for epidemics and for the most severe clinical illness of *Shigella* species. Only SD1 elaborates true Shiga toxin—a neurotoxin and enterotoxin that is associated with the Haemolytic Uremic Syndrome.
(HUS). All *Shigella* species secrete enterotoxins responsible for the watery diarrhoea.

**Clinical Features**
Causes a spectrum of illness from watery diarrhoea to classical dysentery.

The spectrum of disease severity varies according to the host’s immunity and serogroup of the infecting organism. *S. sonnei* commonly causes mild disease, which may be limited to watery diarrhoea, while *S. dysenteriae* or *S. flexneri* commonly causes dysenteric symptoms. In a normal healthy host, the course of disease is generally self-limited, lasting no more than seven days when left untreated.

- **Diarrhoea:** Sudden onset; initial voluminous watery stool (small intestine phase); subsequently containing blood and mucus (colonic phase); fluid depletion typically uncommon.
- **Fever**
- **Nausea. Occasionally vomiting**
- **Abdominal cramps**
- **Tenesmus (common)**
- **Stools usually contain blood and mucous (dysentery)**
- **Painful rectal examination by proctoscopy and the rectum may be hyperaemic or ulcerated.**

**Complications**
- **Intestinal:**
  - Proctitis/rectal prolapse
  - Toxic megacolon
  - Intestinal obstruction
  - Colonic perforation
  - Protein losing enteropathy
- **Systemic:**
  - Reactive arthritis: May follow after *S. flexneri* infection. Can be seen alone or in association with conjunctivitis and urethritis (formerly known as Reiter’s syndrome). HLA-B27 associated.
  - Haemolytic-uremic syndrome in Shiga toxin producing strains.
  - Neurological (seizure, headache, encephalopathy, lethargy, confusion)

**Investigations**
- **Stool leukocytes and culture (select portion with blood or mucus) or rectal swab** (if the patient is unable to provide a stool specimen). *Shigella* is a fastidious organism; and requires prompt handling. Antibiotics susceptibility testing is needed for all specimens.
Blood cultures are usually negative

**Notification**
If two or more cases are recognised in an institution, this should be reported to the Ministry of Health (Form MD 131 or electronically via CD-LENS). Shigellosis is no longer a notifiable disease.

**Management**
- Mild infections are usually self-limited and most patients recover without antibiotic treatment.
- Anyone whose stool cultures are positive for *Shigella* should be treated for public health reasons.
- Antibiotics shorten the duration of fever, diarrhoea and shedding of *Shigella* in stool.
- Treatment regimens include:
  - Ciprofloxacin 500 mg bd x 5 days (Recommended)
  - Azithromycin 500 mg day1, then 250mg daily x 4 days (Alternative)
  - IV Ceftriaxone 1-2 gm daily for hospitalized patients
- Anti-diarrhoeal agents can make the illness worse and should be avoided.

**Infection control**
Contact precautions should be observed when nursing a patient with shigellosis. This involves strict hand-washing before and after handling the patient as well as wearing of personal protective garments e.g. plastic aprons. Proper handling and disposal of stool is important as the organism is present in large amounts in the stool.

Food handlers infected with *Shigella* must be treated with antibiotics and should not be involved in preparation of food as long as their stool cultures are positive; conversion of the stool to negative generally requires at least 48 hours of antibiotic treatment. Health care and day care centre workers should always be treated as well.

**Prevention and Control**
- The Ministry of Health will carry out epidemiological investigations to trace the source of infection when an outbreak is suspected.
- Contacts and food handlers will be screened for *Shigella* and those found to be infected will be treated.
- A high standard of personal and food hygiene is important in preventing transmission.
References


SMALLPOX

Causative Agent
Variola virus, a species of Orthopoxvirus

Incubation Period
12-14 days (range 7-17 days)

Infectious Period
From fever onset (usually 2–4 days before rash) until last scab has separated; about three weeks.

Transmission
Aerosols/droplets from nasopharyngeal lesions and contact with contaminated articles.

Epidemiology
Last naturally acquired human case in the world occurred in Somalia in 1977; global eradication was certified two years later.

There are at least 2 strains, variola major and the variola minor.

- Variola major: the more severe form with case fatality rate up to 30-50% in susceptible populations.
- Variola minor: milder form of the disease with more diminutive pox lesions; case fatality rate of 1-2% in susceptible populations.

Clinical Features
- Characteristic rash appears 2-4 days after non-specific, flu-like prodrome (fever and headache).
- Maculopapular rash begins on mucosa of mouth and pharynx, face, hands, forearms and spreads to legs and centrally to trunk; lesions are more predominant on the face and extremities than on the trunk (centrifugal).
- Lesions progress synchronously on any given part of the body from macules to papules to vesicles to pustules and to crusty scabs.
- Two rare forms of invariably fatal smallpox have been reported:
  - Purpura variolosa or hemorrhagic type smallpox
  - Flat type smallpox

Differential diagnosis
- Chickenpox, monkeypox, disseminated herpes zoster.
- Clues to distinguish smallpox from chickenpox:
  - Smallpox lesions are synchronous in their stage of development
- Smallpox has many more lesions on the face and extremities than trunk (centrifugal spread)
- Smallpox lesions are more common on palms and soles
- Smallpox lesions are more deeply imbedded in the dermis compared with the superficial lesions of chickenpox

Investigations
- Electron microscopy, PCR, viral isolation (culture of pharyngeal swab or lesions).
- Guarnieri bodies on Giemsa or modified silver stain.

Management
- Supportive care.
- Antibiotics may be used for secondary bacterial infection.

Prophylaxis
Vaccination within 3 days of exposure may significantly ameliorate or prevent smallpox. Vaccination 4 to 7 days after exposure likely still offers some protection or modification of disease severity.

Notification
Notify MOH immediately on suspicion. Call MOH Communicable Diseases Surveillance team at: 98171463

Isolation Precautions
- Airborne and contact precautions. Isolate patients in negative pressure isolation room.
- Patients should be considered infectious until all scabs separate and should be isolated during this period.
- Droplet and airborne precaution for a minimum of 17 days following exposure for all persons in direct contact with the index case.

References
TUBERCULOSIS (TB)

Causative Agent
*Mycobacterium tuberculosis* (rarely *M. bovis*).

Incubation Period
Weeks to years

Initial infection usually goes unnoticed—latent TB infection (LTBI). Approximately 10% of those with LTBI will eventually progress to active disease, and half will do so in the first 2 to 3 years following infection. Immunocompromised patients (e.g. HIV infection, diabetes mellitus) are at higher risk for developing active TB.

Infectious Period
Sputum bacteriologically positive, drug-susceptible pulmonary TB is considered non-infectious after two weeks of effective therapy. (Multi-drug resistant TB may require a longer period of effective therapy before cases become non-infectious).

Non-pulmonary TB (except for laryngeal TB) is not infectious.

Transmission
Airborne. Rarely through unpasteurized milk (*M. bovis*).

Epidemiology
- The TB incidence in the local Singapore population (i.e. citizens and permanent residents) rose for the first time in ten years to 40 per 100,000 in 2008 and 39 per 100,000 in 2009. Prior to this, the TB rate of the local population had declined steadily from 57 per 100,000 in 1998 to 35 per 100,000 in 2007. TB continued to be a disease of older males. The TB incidence rate among Malays remained the highest among the three main ethnic groups.
- The majority (83.6%) had pulmonary TB. The two commonest extrapulmonary sites were the pleura and the lymphatic system.
- The number of TB cases among foreigners in Singapore has increased since 2005. In 2009, long-term immigration pass holders comprised 20.8% and short-term pass holders 21.9% of all notified TB cases in the country.
- In 2009, the proportion of primary drug resistance among new pulmonary TB cases in Singapore residents examined was 6.6%. Streptomycin resistance was the most commonly encountered. The proportion of multi-drug resistant (MDR) tuberculosis among new pulmonary TB cases in Singapore residents examined has remained very low, at 0.3%. The MDRTB rate is, however, 10 or more times higher among foreigners reported with TB in Singapore, i.e. 3% among...
Indonesians and those from the People’s Republic of China, 4% among Vietnamese and 6% among Burmese.

Clinical Features
- Pulmonary TB: Common symptoms are prolonged cough (> 3 weeks), chest pain and haemoptysis. Patients with miliary TB may have minimal respiratory symptoms and present with systemic complaints.
- Extrapulmonary TB: Lymphadenitis (especially cervical), pleural effusion, osteomyelitis, meningitis or gastrointestinal involvement.
- Patients often have associated fever, night sweats, loss of appetite, loss of weight and fatigue.
- Risk factors for HIV and examination for physical signs of HIV (e.g. oral candidiasis) should be sought.

Investigations
- Chest X-Ray. All persons with chest X-ray findings suggestive of TB should have sputum specimens submitted for microbiological examination.
- Acid fast bacilli (AFB) smear and TB culture of sputum and other pathological specimens such as pleural fluid, CSF, urine and pus. All patients suspected of having pulmonary TB should have at least two, preferably three, sputum specimens obtained for microscopic examination and TB culture (with drug susceptibility testing), with at least one early morning specimen where possible.
- Nucleic acid amplification tests (NAATs) do not obviate the need for TB culture as these tests do not provide information on the drug susceptibility pattern of the organism. The NAATs are not sufficiently sensitive for a negative result to exclude TB in smear-negative sputum samples.
- HIV testing should be performed for all patients.
- Screening for diabetes mellitus is strongly recommended.

Notification
- Healthcare providers are required to notify suspected and confirmed cases to the Director, TB Control Unit, c/o STEP Registry (Form MD 532 or electronically via CD-LENS) within 72 hours.
- Attending physicians should also submit Form MD 117, or via CD-LENS, to update treatment progress and changes at each visit, preferably monthly until a final outcome is reached.

Management
- Any physician treating a patient for TB is assuming an important public health responsibility; he must not only prescribe an appropriate regimen but also be
capable of assessing adherence of the patient to the regimen, and addressing poor adherence when it occurs.

- Initial drug therapy for new cases should consist of 4 first-line drugs: isoniazid (INH), rifampicin, pyrazinamide and ethambutol or streptomycin. Initiating treatment using a quinolone as a first-line drug is not a standard practice. In uncomplicated, drug-susceptible TB cases, 6 months of drug therapy is sufficient. Monotherapy should never be given as this will generate drug-resistant TB. A single drug should never be added to a failing regimen.

- The treating physician should be alert to the TB culture and drug susceptibility results which may take several weeks to be available. There should be an index of suspicion for the possibility of drug-resistant TB in patients who were previously treated, who fail treatment, who are known contacts of MDRTB cases, or who come from countries with high prevalence of TB drug resistance.

- Non-adherence because of adverse reactions and prolonged therapy is a major problem. Non-adherence leads to possible treatment failure and acquired drug resistance.

- Directly observed therapy (DOT) is recommended for all TB patients, as it allows for closer monitoring, thus ensuring adherence to treatment, preventing the development of drug resistance. DOT is available at the TB Control Unit (TBCU) and polyclinics.

- All patients should be issued with medical leave for at least two weeks, after which they may be considered non-infectious.

- Follow-up appointments should be at no longer than monthly intervals for patients on TB treatment. Patients should be asked about clinical response to treatment, adherence to therapy and any adverse drug effects, particularly hepatitis. Patients with signs or symptoms suggestive of hepatitis such as jaundice, nausea, loss of appetite, abdominal discomfort, tea coloured urine and easy fatiguability should be further evaluated with liver function studies.

- Response to treatment is best monitored bacteriologically with repeat sputum examination at the very least at two months (end of intensive phase) and at the end of treatment. Those who do not convert their sputum cultures at two months may require extension of treatment duration beyond six months.

- A record of all medications given, bacteriological response, and adverse reactions should be maintained for all patients.

- Sputum smear-positive cases, relapsed cases and those with risk factors for drug-resistant TB should be referred to the TBCU.

- Non-compliance to TB treatment should be detected promptly, and these cases should be referred to TBCU.

**Prevention and Control**

- In an endemic area, BCG vaccination at birth helps to reduce the incidence of miliary TB and TB meningitis in childhood.
Early recognition and early appropriate treatment of TB cases. Suspect TB in any person with unexplained cough for three or more weeks.

In hospitals and other institutions, isolation of smear-positive patients for at least 2 weeks after initiation of appropriate drug therapy will help reduce transmission.

Screening of close contacts of infectious (i.e. sputum bacteriologically positive) TB cases for latent TB infection (LTBI) and preventive therapy. This is performed by the TBCU Contact Clinic.

- The tuberculin skin (Mantoux) test is the standard method of LTBI screening. Criteria for a positive reaction depend on the patient’s health status and TB risk.
- All screened close contacts found to have LTBI should be offered treatment, regardless of age and BCG vaccination status. Before initiating treatment, active TB must be ruled out by patient history, physical examination, and chest X-ray.
- Isoniazid (INH) is the treatment of choice for LTBI. For adults, the recommended duration of treatment is at least six, and preferably, nine months.

**Air Travel**

- According to WHO guidelines, people with infectious or potentially infectious TB should not travel by commercial air transportation on a flight of any duration, until there is no longer a risk of transmitting infection to others.
- Physicians should inform all patients with infectious or potentially infectious TB that they pose a risk of infection to others, and advise them that they must not travel by any public air transportation as long as they are considered infectious or potentially infectious.

**References**

TULAREMIA

Causative Agent
Francisella tularensis

Incubation Period
3 - 5 days (range 1 to 14 days)

Infectious Period
No human-to-human transmission

Transmission
Humans can become incidentally infected through diverse routes of exposures: bites of infective arthropods (primarily ticks and mosquitoes); handling infectious animal tissue or fluids; ingestion of contaminated water, or inadequately cooked meat of infected animals; and inhalation of dust from contaminated soil. Laboratory infections occur through accidental inoculation or by inhaling aerosolized organisms.

Inoculation or inhalation of as few as 10 organisms is needed to cause disease and is one of the most infectious pathogenic bacteria known.

The primary concern for intentional infection by the organism is through inhalation after aerosol dissemination of bacteria.

Epidemiology
The majority of infections in humans and animals are caused by the two species: F. tularensis subspecies tularensis (most virulent) and F. tularensis subspecies holarctica and rarely subspecies philomiragia and novicida.

The disease occurs naturally throughout much of North America and Eurasia. F. tularensis is found in widely diverse animal hosts and habitats and can be recovered from contaminated water, soil, and vegetation. A variety of small mammals, including voles, mice, water rats, squirrels, rabbits, and hares, are natural reservoirs of infection.

Tularemia is almost entirely a rural disease, though exposure in urban or suburban settings does occur. Certain activities, such as hunting, trapping, butchering, and farming, are associated with transmission risk.

The agent for tularemia is not indigenous in Singapore. Bioterrorism should be suspected should this disease be diagnosed in Singapore in persons without a relevant travel history.
Clinical Features

- Clinical forms vary in presentation and severity depending on virulence of the infecting organism, dose and site of inoculation.

- Main forms of disease:
  
  Pneumonia:
  - Pleuropneumonitis with hilar lymphadenitis (through airborne or haematogenous routes).
  - Occurs more often in the elderly and has a higher mortality rate.
  - Radiographic features of tularemic pneumonia include patchy unilateral or bilateral infiltrates, lobar or segmental opacities, hilar adenopathy, pleural effusions, cavitary lesions and occasionally a miliary pattern.

  Ulceroglandular (60-80%):
  - Patients typically present with fever and a single erythematous papuloulcerative lesion with a central eschar accompanied by tender regional lymphadenopathy.
  - Patients usually report recent handling of an animal, an animal bite (especially cat bites), or exposure to potential vectors, particularly ticks.

  Oculoglandular (1-2%):
  - Chemosis /conjunctivitis with regional lymphadenitis (through inoculation of conjunctiva).

  Oropharyngeal (1-4%):
  - Exudative pharyngitis/tonsillitis with cervical adenitis (through inoculation of oropharyngeal mucosa).
  - Diagnosis should be considered in patients with pharyngitis unresponsive to penicillin.

  Glandular (3-15%):
  - Enlargement of a single or multiple lymph nodes without an identifiable skin lesion.

  Typhoidal:
  - Typhoidal tularemia with or without pneumonia is an uncommon presentation.
  - Systemic illness with non-localizing fever.

- Onset of illness is usually abrupt, with fever (38°- 40°C), headache, chills, coryza and sore throat. Pulse-temperature dissociation has been noted in as many as 42% of patients.

- A dry or slightly productive cough and substernal pain or tightness frequently occur with or without objective signs of pneumonia, such as purulent sputum, dyspnoea, tachypnoea, pleuritic pain, or haemoptysis.
Nausea, vomiting, and diarrhoea sometimes occur. Sweats, fever and chills, progressive weakness, malaise, anorexia, and weight loss characterize the continuing illness.

Any form of tularemia may be complicated by hematogenous spread, resulting in secondary pleuro-pneumonia, sepsis and rarely, meningitis.

**Investigations**
The laboratory needs to be notified for special diagnostic and safety procedures.

- Direct examination of secretions, exudates and biopsy specimens using Gram stain, direct fluorescent antibody or immunochemical stains.
- Culture of *F. tularensis* from clinical specimens (pharyngeal washings, sputum or fasting gastric aspirates).
- Serology with a fourfold titre change of serum antibodies against *F. tularensis*.

**Management**

**In contained casualty setting:**

Drugs of choice:
- IM streptomycin 1gm 12 hourly for 10 days; *or*
- IV/IM gentamicin 5mg/kg once daily for 10 days

Alternatives:
- IV doxycycline 100 mg 12 hourly for 14-21 days; *or*
- IV ciprofloxacin 400 mg 12 hourly for 10 days

**In mass casualty setting:**

Drugs of choice:
- Doxycycline 100 mg orally 12 hourly for 14-21 days; *or*
- Ciprofloxacin 500 mg orally 12 hourly for 10 days

**Chemoprophylaxis**
Exposed persons can be prophylactically treated with 14 days of oral doxycycline or ciprofloxacin. If unexplained fever or flu-like illness develops within 14 days of exposure, then treat as for infection.

**Notification**
Notify MOH immediately on suspicion. Call MOH Communicable Diseases Surveillance team at: 98171463

**Vaccine**
Currently no vaccine is available locally. In the United States, a live attenuated vaccine has been used by laboratory staff working routinely with the bacterium.
**Isolation Precautions**

Standard precautions are recommended. Respiratory isolation is not necessary given the lack of human-to-human transmission. Bodies of patients who die of tularemia should be handled using standard precautions. Autopsy procedures likely to produce aerosols or droplets should be avoided.

**References**

TYPHOID AND PARATYPHOID FEVER

Causative Agents
Salmonella typhi (Typhoid fever)
Salmonella paratyphi A, B and C (Paratyphoid fever).

Incubation Period
1 - 3 weeks

Infectious Period
During acute infection and until stool and urine clearance.

Transmission
Faeco-oral route through contaminated food or water. Transmission through sexual contact, especially among men who have sex with men have been documented. There is no animal reservoir so ultimately the disease always involves human-to-human spread.

Epidemiology
During the period 2005-2009, there were 349 reported cases of typhoid (94% imported) and 139 reported cases of paratyphoid (88.5% imported). The disease is endemic in Southeast Asia and the Indian subcontinent.

Clinical Features
■ Typhoid fever
  ▪ 1\textsuperscript{st} week of illness: Rising, “stepwise” fever, bacteraemia and diarrhoea (78% of children) or constipation (more frequent in adults).
  ▪ 2\textsuperscript{nd} week of illness: Abdominal pain and rash (rose spots)
  ▪ 3\textsuperscript{rd} week of illness: Hepatosplenomegaly, intestinal bleeding and perforation

■ Complications (rare if diagnosed and treated early)
  ▪ Intestinal haemorrhage or perforation
  ▪ Toxic myocarditis
  ▪ Confusion, convulsions, encephalitis
  ▪ Haemolytic anaemia (especially in G6PD deficiency)
  ▪ Renal failure
  ▪ Abscesses in liver, spleen, bone etc.

■ Paratyphoid fever
  ▪ Maybe clinically mild or asymptomatic
- Nausea, vomiting, fever, diarrhoea, and cramping—usually occur within 8 to 72 hours of ingesting contaminated food or water
- Less than 5% of non-typhoidal salmonella gastroenteritis develop bacteraemia and may result in extra-intestinal manifestations including endocarditis, mycotic aneurysm and osteomyelitis.

**Investigations**
- Blood test frequently show anaemia, elevated hepatic transaminases and either leucopenia or leucocytosis.
- Isolation of organism is the gold standard for diagnosis.
- Blood culture usually positive for 1st two weeks only.
- Stool and urine culture positive from 2\(^{nd}\) to 4\(^{th}\) weeks.
- The yield from bone marrow culture is high and is usually positive even after antibiotics have been initiated.
- The Widal test is unreliable in itself, but may provide additional support for the diagnosis when the clinical picture is suggestive.

**Notification**
A legally notifiable disease in Singapore. Notify Ministry of Health (Form MD 131 or electronically via CD-LENS) not later than 24 hours from the time of diagnosis.

**Management**

**Typhoid**
- Patients should be hospitalised during antibiotic treatment.
- Rehydration and other supportive care.
- Current drugs of choice:
  - PO Ciprofloxacin 500 mg bd x 7-10 days (if sensitive to ciprofloxacin and nalidixic acid)
  - IV Ceftriaxone 2-3g once daily x 10-14 days
  - Alternative: PO Azithromycin 1g once then 500mg once daily x 5-7 days
  - N.B. 70-90 % of isolates in some parts of Nepal, India and Vietnam are nalidixic acid resistant strains.
- Dexamethasone 3mg/kg then 1mg/kg 6 hourly x 8 doses for severe typhoid fever (as suggested by delirium, shock and altered mental status) decreases mortality.
- Relapse rate 1-6% with newer antibiotics (10-25% with chloramphenicol)
- One to four percent of adults become chronic carriers despite antibiotics.
- Follow-up stool evaluation to document stool clearance after treatment:
  - Three consecutive stool samples taken at weekly intervals no sooner than two weeks after completion of antibiotic treatment.
- Chronic carriers (positive stool samples after 6 months): give prolonged course of ciprofloxacin (750 bd orally for 1 month) and perform abdominal ultrasound; cholecystectomy may be necessary if gallstones are present and prolonged antibiotic treatment fails.

**Prevention and Control**

- Public health measures: education on good personal and food hygiene.
- Vaccination for travellers: (see section on travel vaccination in Appendix 3).
- Follow up stool examinations recommended for all cases and mandatory for food handlers.
- Food handlers require further stool examination (three consecutive daily stool samples) at three and six months post treatment.
- Carriers (convalescent, temporary and chronic) must not work as food handlers.

**References**