

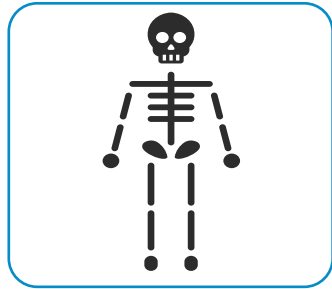
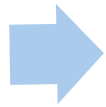


# THE BODY SYSTEM IN LEGIONELLOSIS

Ayoung Hong

<https://www.newsweek.com/legionella-bacteria-symptoms-duke-university-outbreak-1621390>

# TABLE OF CONTENTS



## Clinical presentation

- Signs
- Symptoms
- History of present illness
- Possible presentation that are not in the case

## Affected Body systems

- Respiratory system
- Other systems: extrapulmonary

## Treatment: Antibiotics

- Principles of Therapy
- Quinolones
- Azithromycin
- Doxycycline

## Others

- Significance of hot tub exposure
- Life cycle of *Legionella*
- Reportable communicable disease
- Identification of source

# CASE AND LEGIONELLOSIS

## CASE

To celebrate Tom's retirement his wife and two adult children accompany him on a long anticipated cruise. Tom's asthma flares up a few days before the cruise but with a corticosteroid nebulizer he feels well enough to join the cruise. Even more than the rest of his family, Tom enjoys the various hot tubs aboard the massive ship those first few days, relishing the relaxation after a busy final year at work. On the fifth day of the cruise, Tom wakes up in a sweat with a cough that continues throughout the day. As the day wears on he feels worse with a headache, muscle aches and nausea accompanying the cough. His wife arranges for the cruise doctor to visit him in his cabin. The doctor examines Tom, notes his high temperature, nonproductive cough and recent history of asthma and corticosteroid therapy. She takes a full history including taking note of his activities during the first days of the cruise and diagnoses Tom with pneumonia. She starts Tom on azithromycin. By the time the ship returns to port two days later, 5 more people have been diagnosed with a similar pneumonia, several of whom have a slightly compromised immune system, as Tom does. One of the others is admitted to hospital, where sputum and urine samples are tested and reveal a diagnosis of **Legionellosis**. Public health authorities are notified and the ship takes extra time in port to allow for an enhanced cleaning to be performed on all of the hot tubs.

## Types of Legionellosis (1)

1. Legionnaires' disease: Tom's case, pneumonic and severe
2. Pontiac Fever: non-pneumonic and less severe, mild flu-like



# CLINICAL PRESENTATION

# CLINICAL PRESENTATION IN THE CASE

## Signs

- No clinical signs specific to Legionellosis

## Symptoms

- Tom experienced night sweat, non-productive (dry) cough, fever, headache, muscle aches, nausea.

## Key history of presenting illness elements presented

- Location: systemic (fever, headache, muscle aches), lungs (pneumonia)
- Quality: not specified
- Quantity/severity: not specified
- Timing: On the fifth day of his cruise, the first symptom started as he woke up with sweat and cough. His symptoms persisted for the remaining two days of cruise.
- Setting: Tom got infected in the cruise ship probably because he used hot tub often. *Legionella* infection occurs via ingestion of infected water, or inhalation of infected aerosolized water. (1, 2)
- Factors: male gender, chronic lung disease (predisposed asthma and flare-up), immunosuppressive agent (recent corticosteroid use) (1)
- Association manifestations: pneumonia



# NOT IN THE CASE, BUT COULD HAVE BEEN PRESENTED IN LEGIONELLOSIS

## Signs

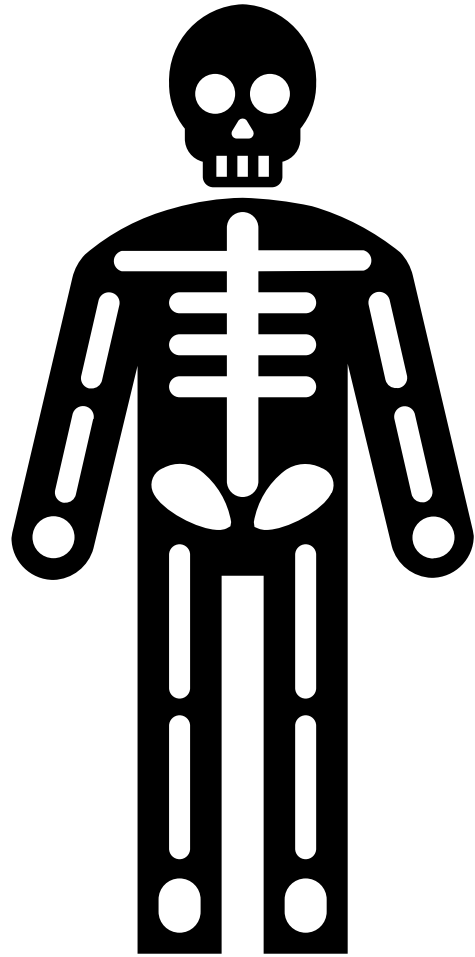
- Non-specific to Legionellosis: hyponatremia, hypophosphatemia, elevated liver enzymes, leukopenia, leukocytosis, pyuria, elevated creatine kinase (1)

## Symptoms that are not in the case, but could have been presented:

- extrapulmonary symptoms: malaise, lack of appetite, lethargy, vomiting, diarrhea, seizures, and bradycardia, (1, 2)
- Pulmonary symptoms: cough with purulent sputum, pleuritic chest pain, difficulty breathing (1, 2)

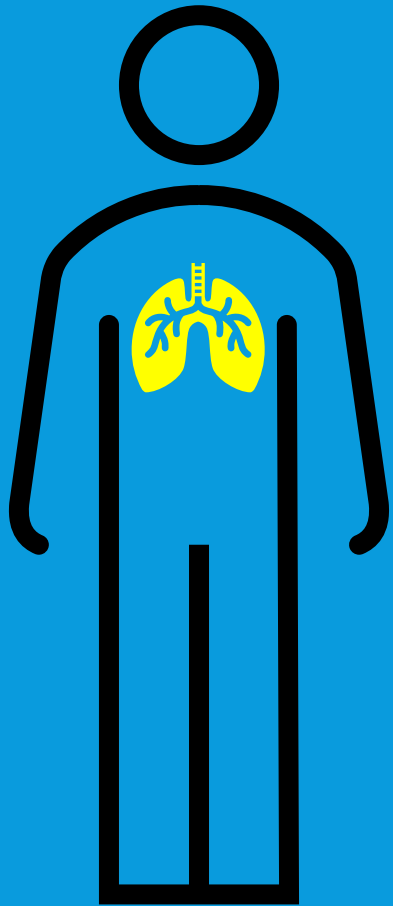
## History of illness

- Timing-Incubation period
  - Pneumonic Legionnaire's Disease: between 2-10 days, median 4-6 days (outliers 1-28 days), 10% of epidemic cases had longer than 10 days (1)
  - Non-pneumonic Pontiac fever: 4 hours-3 days (median 32-36 hours) (1)
- Setting
  - cooling tower, water spa, water fountain, or water mister (1)
  - Nosocomial transmission: nasogastric tube, humidifier, ventilator tubing, and nebulizers treated with tap water instead of sterile water(1)
- Factors: Male gender, cigarette smoking, chronic heart/lung disease, diabetes, end-stage renal disease, organ transplantation, immunosuppression, cancer, age greater than 50 years
- Association manifestations: pneumonia, Pontiac fever, extrapulmonary infection (1)



AFFECTED  
BODY SYSTEMS

# AFFECTED BODY SYSTEMS: RESPIRATORY SYSTEM



## Entry

- Commonly, via inhalation of aerosolized water infected with *Legionella pneumophila* (1, 2, 3)
- Rarely, via contact of infected water to wound (3)

## Multiplication

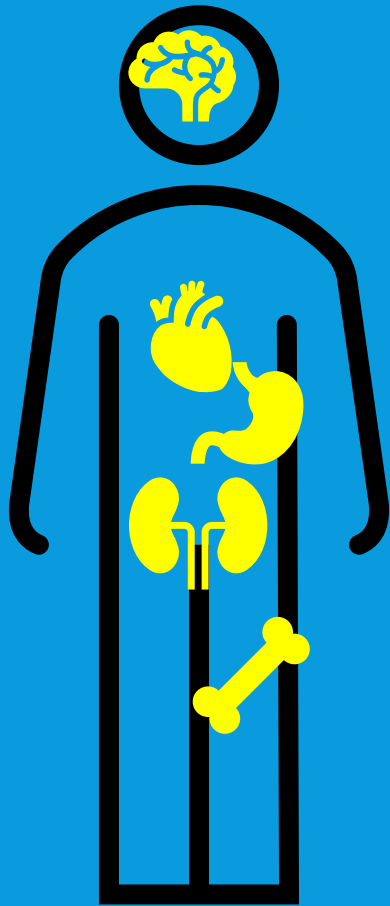
- Inhaled water arrives at trachea and infect tissues. *L. pneumophila* replicates at upper respiratory tract, then spreads to lower respiratory tract.
- At lungs, alveolar macrophages recognize pathogen-associated molecular patterns (PAMPs) with toll-like receptors (TLRs). Innate immune cells initiates an inflammatory response by releasing pro-inflammatory cytokines (TNF- $\alpha$ , IL-12, IL-18, IFN- $\gamma$ ). (1)  
Release of these cytokines recruits more immune cells to the site of infection. (1)
- Increased infiltration of immune cells increases cellular permeability and fluid leakage. Capillary leakage results in edema. (1)

## Pneumonia

- Accumulated cellular debris, serum, and fibrin destroy air spaces in alveoli. (1, 3)
- Result is impaired gas exchange. (1, 4) Compromised respiratory function result in cough, pleuritic chest pain, and difficulty breathing (1, 3)



# AFFECTED BODY SYSTEMS: OTHER EXTRAPULMONARY SYSTEMS



- **Spreads to other system:** rare. (3, 4) If the *L. pneumophila* survives intracellularly within macrophage (i.e., if infection is not cleared quickly), the pathogen can spread to other organs and start disseminated infection. (1, 2, 3)
- **Extrapulmonary infections:** occur mostly in immunocompromised patients (1)
  - Central nervous system: brain (1)
  - Immune system: extrathoracic lymph nodes, spleen, bone marrow (1)
  - Cardiovascular system: myocardial muscles, vascular shunts and graft, heart valves (1)
  - Gastrointestinal system: intestine (1)
  - Urinary system: kidney (1)
  - Musculoskeletal system: joint, skeletal muscle (1)



# TREATMENTS: ANTIBIOTICS

# PRINCIPLES OF ANTIBIOTIC THERAPY

## Therapy in pneumonia

- Empiric therapy of community-acquired pneumonia (CAP) includes  $\beta$ -lactam, macrolide plus  $\beta$ -lactam, or fluoroquinolone. (5)
- The doctor prescribed Macrolide (azithromycin) to Tom. Azithromycin was given as empiric therapy, because culture was not available yet. Macrolide can cover many causative organisms of pneumonia including *S. pneumoniae* (if penicillin susceptible), *H. influenzae*, *Legionella* species, *M. pneumoniae*, *C. pneumoniae*, *C. burnetii*. (5)

## Principles of Therapy in Legionellosis

- Antibiotics should be concentrated and bioactive within the subcellular location, because *L. pneumophila* resides within the phagocytes. (1, 2) quinolones, macrolides, and tetracyclines are effective to treat legionellosis. (1, 2)
- First-line therapy: Preferred drug of choices are fluoroquinolones and macrolide. (1, 4)
- Alternative option: doxycycline (1, 2, 4)
- $\beta$ -lactams, monobactams, aminoglycoside, or phenicols are ineffective to treat legionellosis (1, 2)

# QUINOLONES

## (LEVOFLOXACIN, CIPROFLOXACIN, MOXIFLOXACIN)

### Mechanism of Action

- Fluoroquinolones (FQ) inhibit DNA-gyrase (topoisomerase II). Topoisomerases relax the supercoiling of DNA. (6)
- FQ breaks DNA and inhibits DNA synthesis in bacteria. (6) Arrested DNA replication results in bacterial death. (6)
- Ciprofloxacin has gram-negative coverage. (6) Respiratory quinolones, levofloxacin and moxifloxacin, have additional coverage of gram-positive bacteria. (6)
- In pneumonia, quinolone monotherapy can cover broadly both typical and atypical bacteria. (6, 7)
- Quinolone monotherapy is shown to be superior to macrolide or doxycycline in pneumonia caused by *Legionella*. (1, 5, 6)

### Treatment Regimen

- In mild pneumonia, outpatient, not immunocompromised: Levofloxacin 500mg daily, OR ciprofloxacin 500mg twice daily, OR moxifloxacin 400mg daily for 7-10 days (1, 5)
- In moderate to severe pneumonia or immunocompromised: Levofloxacin 500mg daily for 7-10 days, OR ciprofloxacin 400mg intravenously three times a day then 750mg orally twice a day for 10-14 days, OR Moxifloxacin 400mg daily for 10-14 days

# MACROLIDES (AZITHROMYCIN)

## Mechanism of Action

- Macrolides bind to 23S rRNA of the 50s ribosomal subunit in bacterial protein synthesis complex. (8)  
Hence, macrolides inhibit bacterial protein synthesis. (8)
- Azithromycin accumulates in phagocytes and distributes highly compared to other macrolides. (9) It penetrates cell membranes and fights against gram-negative bacteria effectively. (9)

## Treatment Regimen

- In mild pneumonia, outpatient, not immunocompromised: Azithromycin 500mg daily for 3-5 days (1, 5)
- In moderate to severe pneumonia or immunocompromised: Azithromycin 500mg daily for 5-7 days (1, 5)

# TETRACYCLINE (DOXYCYCLINE)

## Mechanism of Action

- Doxycycline binds to 30S and 50S subunits of bacterial ribosomes. (10) These bindings inhibit bacterial protein synthesis. (10)

## Treatment Regimen

- In mild pneumonia, outpatient, not immunocompromised: Doxycycline 200mg loading dose, then 100mg twice daily for 10-14 days (1)
- In moderate to severe pneumonia: 400mg daily for 3 days, then 200mg daily (7)



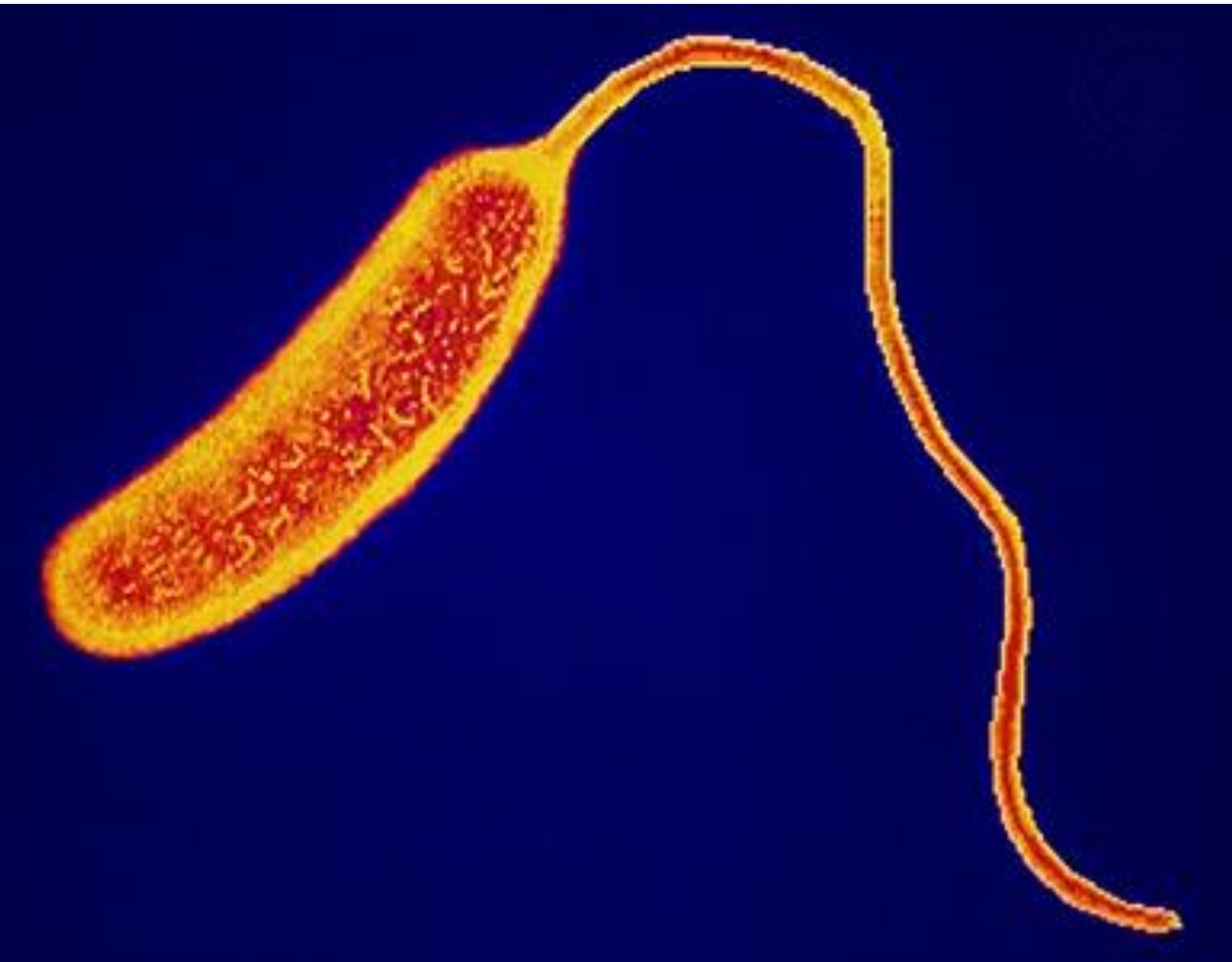
# TETRACYCLINE (DOXYCYCLINE)

## Mechanism of Action

- Doxycycline binds to 30S and 50S subunits of bacterial ribosomes. (10) These bindings inhibit bacterial protein synthesis. (10)

## Treatment Regimen

- In mild pneumonia, outpatient, not immunocompromised: Doxycycline 200mg loading dose, then 100mg twice daily for 10-14 days (1)
- In moderate to severe pneumonia: 400mg daily for 3 days, then 200mg daily (7)



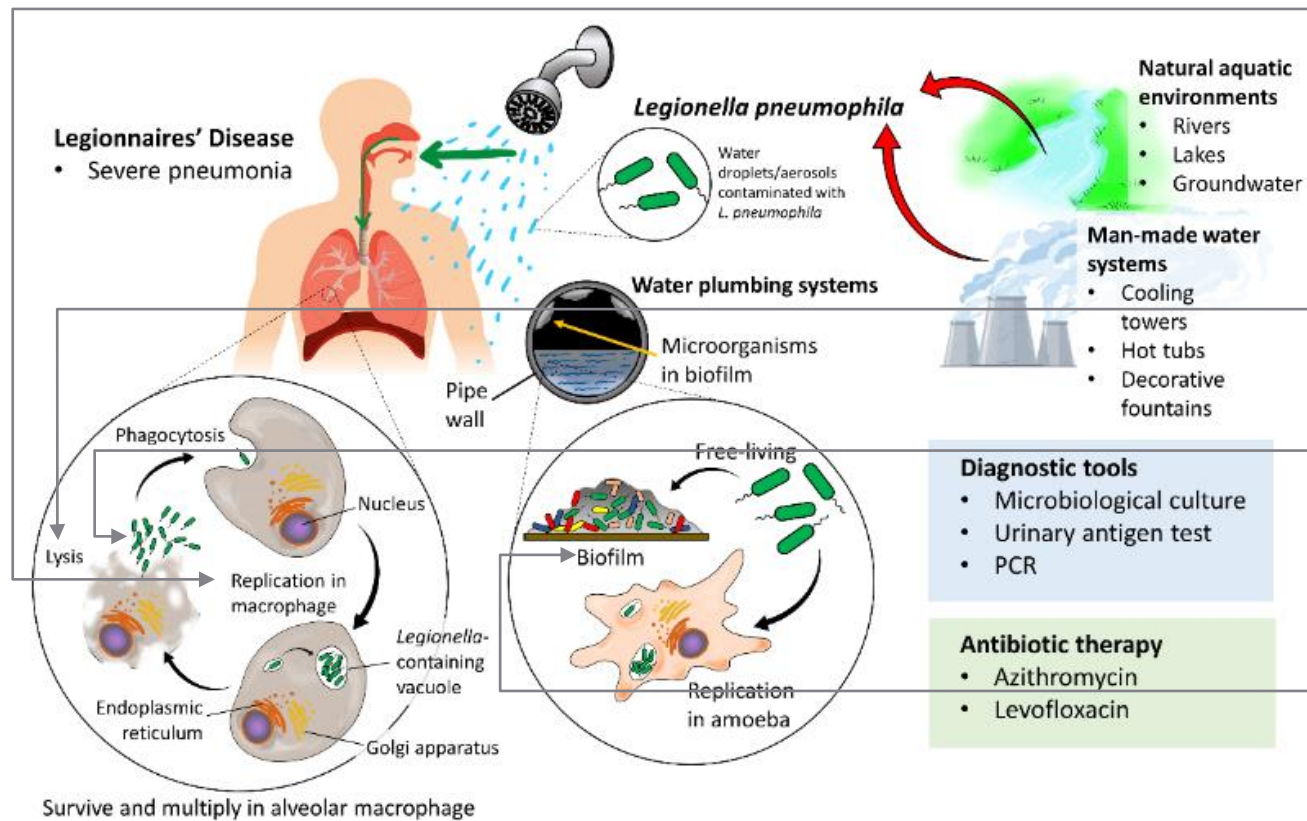
[This Photo](#) by Unknown Author is licensed under [CC BY-NC](#)

# OTHERS

# SIGNIFICANCE OF THE EXPOSURE TO HOT TUBS

- In Tom's case, hot tub is the likely source of Infection. He also used hot tubs often.
- *Legionella* species are environmental bacteria that originate from water or soil. (1, 3) The major reservoir of *Legionella* is warm water that is 25-40 Celsius. (1)
- In nature, *Legionella* reside within free-living amoebae. (1, 3) Amoeba occurs in same aquatic environment and supports *Legionella's* survival. (3)
- *Legionella* is relatively resistant to the effects of chlorine and heat. (1, 3)
- Ability of *Legionella* to survive within the amoebae and relatively hot aquatic environment, combined with chlorine resistance makes the hot tub the most probable source of infection in Tom's case.

# LIFE CYCLE OF *Legionella*



## • Replicative Phase

- When nutrients are abundant, survive within the cell (amoeba/macrophage), (1, 3, 11)
- Non-motile and multiplies until nutrition-depleted (1, 3)

## • Depletion of Nutrient → Cell (amoeba/macrophage) lysis (1, 3, 11)

## • Transmissive phase

- In nutrient-poor environment, *Legionella* is motile and seeks for other amoeba/macrophages to invade (1, 3, 11)

## • Biofilm of amoeba in water systems

- Amoeba infected with *Legionella* can form biofilm in water systems. (1, 11)
- Biofilm gives additional protection (1, 11)

Life cycle of *Legionella pneumophila* within water systems and human macrophage. (11)

# REPORTABLE COMMUNICABLE DISEASE

## In British Columbia

- Legionellosis is a reportable communicable disease under the BC Public Health Act. (12)
- Physicians and laboratories must report cases to the Medical Health Officer (MHO). (12)
- Only Confirmed cases: clinical illness with laboratory confirmation of infection (12)
  - Laboratory confirmation includes,
    - Isolation of *Legionella* species from bodily fluids that are normally sterile (12) OR
    - 4 times or more of rise in *Legionella* species IgG titre between acute and convalescent sera (12) OR
    - Seroconversion from non-reactive IgG, IgM reactive or from IgM reactive to IgG reactive (12) OR
    - *L. pneumophila* antigen in urine (12) OR
    - *Legionella* species DNA by NAT from bodily fluids that are normally sterile (12)
- If a case is occupationally-related, WorkSafeBC should be informed. (12)

# IDENTIFICATION OF BACTERIAL SOURCE

- In BC, confirmed cases of legionellosis will be interviewed by Regional Health Authority public health staff. (12)
- By interview, source of infection can be identified. (12) Education on further prevention can be provided as well. (12) Interview should be attempted within 3 business days of case notification.
- Cases can be divided into three categories, healthcare/long-term facility-related cases, travel-related cases, and community-acquired occupational and other cases. (12)
- Single case investigation: obtaining the exposure history of patient
- Outbreak investigation
  - Environmental investigation: site assessment, inspection of systems, environmental sample collection (12)
  - Microbiological investigation: clinical samples testing, environmental sample testing (12)
- If evidence is not sufficient to identify the source, hypothesis can be established and tested. (12)
- After the identification of the source, long-term preventative measures (e.g., enhanced cleaning), post-outbreak monitoring, and debrief and report of outbreak will be done. (12)



# REFERENCES

1. Edelstein PH, Roy CR. Chapter 232. Legionnaires' Disease and Pontiac Fever. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA: Elsevier; 2020.
2. Cunha BA, Burillo A, Bouza E. 2016. Legionnaires' disease. *Lancet* 387(10016): 376-385. [https://doi.org/10.1016/S0140-6736\(15\)60078-2](https://doi.org/10.1016/S0140-6736(15)60078-2)
3. Winn WC Jr. Legionella. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 40. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK7619>
4. DynaMed. Legionella Infections. EBSCO Information Services. Accessed March 22, 2023. <https://www.dynamed.com/condition/legionella-infections>
5. Loeb, Mark. Community-Acquired Pneumonia. In: e-CTC[Internet]. Ottawa (ON): Canadian Pharmacists Association. C2023[updated 2022, May 02; cited 2023 Mar 22]. Available from: <http://www.myrxtx.ca>. Also available in paper copy from the publisher.
6. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Associations, c2023[updated 2018, Mar 01; cited 2023 Mar 22]. Fluoroquinolones [CPhA monograph]. Available from: <http://www.myrxtx.ca>. Also available in paper copy from the publisher.
7. Cunha, B A. "The atypical pneumonias: clinical diagnosis and importance." *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* vol. 12 Suppl 3 (2006): 12-24. doi:10.1111/j.1469-0691.2006.01393.x
8. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Associations, c2023[updated 2019, Mar 05; cited 2023 Mar 22]. Azithromycin [CPhA monograph]. Available from: <http://www.myrxtx.ca>. Also available in paper copy from the publisher.
9. Parnham MJ, Haber VE, Giamarellou-Bourboulis EJ, Perletti G, Verleden GM, Vos R. 2014. Azithromycin: Mechanisms of action and their relevance for clinical applications. *Pharmacology & Therapeutics* 143:225–245
10. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Associations, c2023[updated 2018, Jan 08; cited 2023 Mar 22]. Tetracyclines [CPhA monograph]. Available from: <http://www.myrxtx.ca>. Also available in paper copy from the publisher.
11. Tan LT, Tee WY, Khan TM, Ming LC, Letchumanan V. Legionella pneumophila—The causative agent of Legionnaires' disease. *Progress In Microbes & Molecular Biology*. 2021 Apr 8;4(1).
12. BC Center for Disease Control. 2021. Chapter I – Management of Specific Diseases Legionella outbreak investigation and control. Retrieved from <http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%201%20-%20CDC/BC%20Legionella%20Guidelines%202021%20July%20FINAL.pdf>