



A Chronic Cough

# The Body System

## • Similar to cold-like symptoms:

○ → Mild cough

○ → Runny nose

○ → Low grade fever

○ → Apnea – a pause in breathing (in babies)

### Disease Progression: Pertussis

Weeks

0 1 2 3 4 5 6 7 8 9 10 11 12

**Stage 1  
Catarrhal Stage**  
*May last 1 to 2 weeks*

– Symptoms: runny nose, low-grade fever, mild, occasional cough – Highly contagious

**Stage 2 - Paroxysmal Stage**  
*Lasts from 1-6 weeks; may extend to 10 weeks*

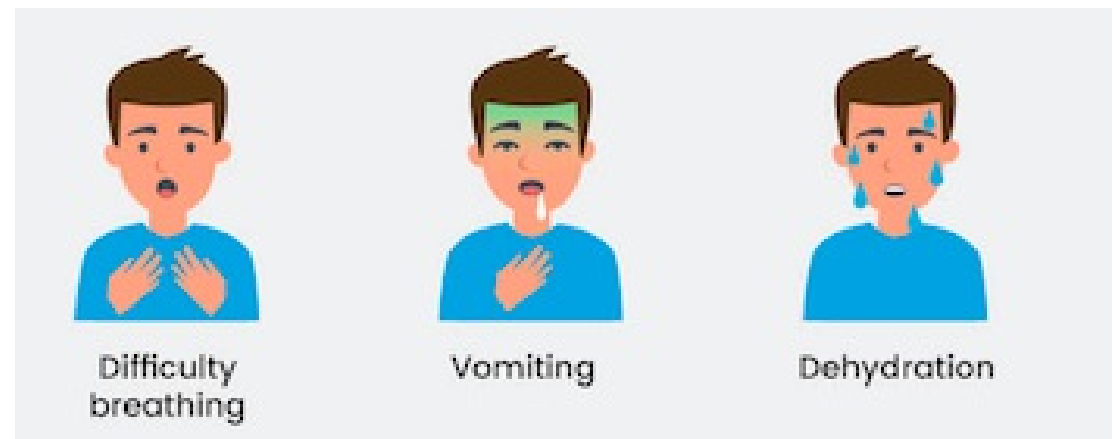
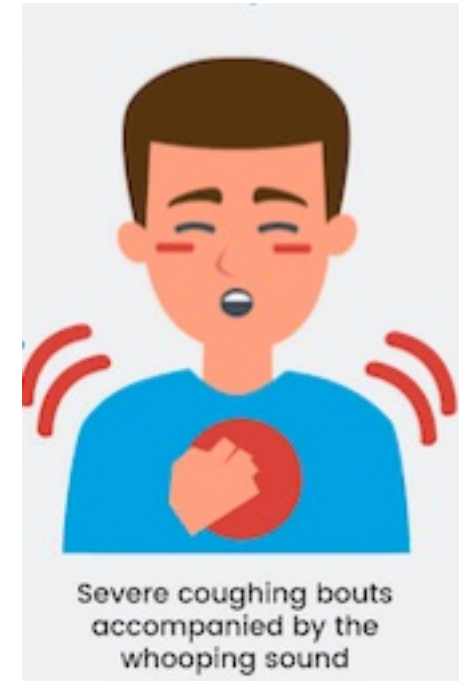
Symptoms: fits of numerous, rapid coughs followed by "whoop" sound; vomiting and exhaustion after coughing fits (called paroxysms)

**Stage 3 - Convalescent Stage**  
*Lasts about 2-3 weeks; susceptible to other respiratory infections for many*

Recovery is gradual. Coughing lessens but fits of coughing may return.

# Later stage symptoms (after 1-2 weeks)

- Paroxysms (fits) of coughs followed by a “whoop” sound. This happens because constant coughing deprives your lungs from air until there is no more and your lungs are forced to inhale with a loud whooping sound.
- Vomiting during or after coughing fits
- Exhaustion after coughing fits

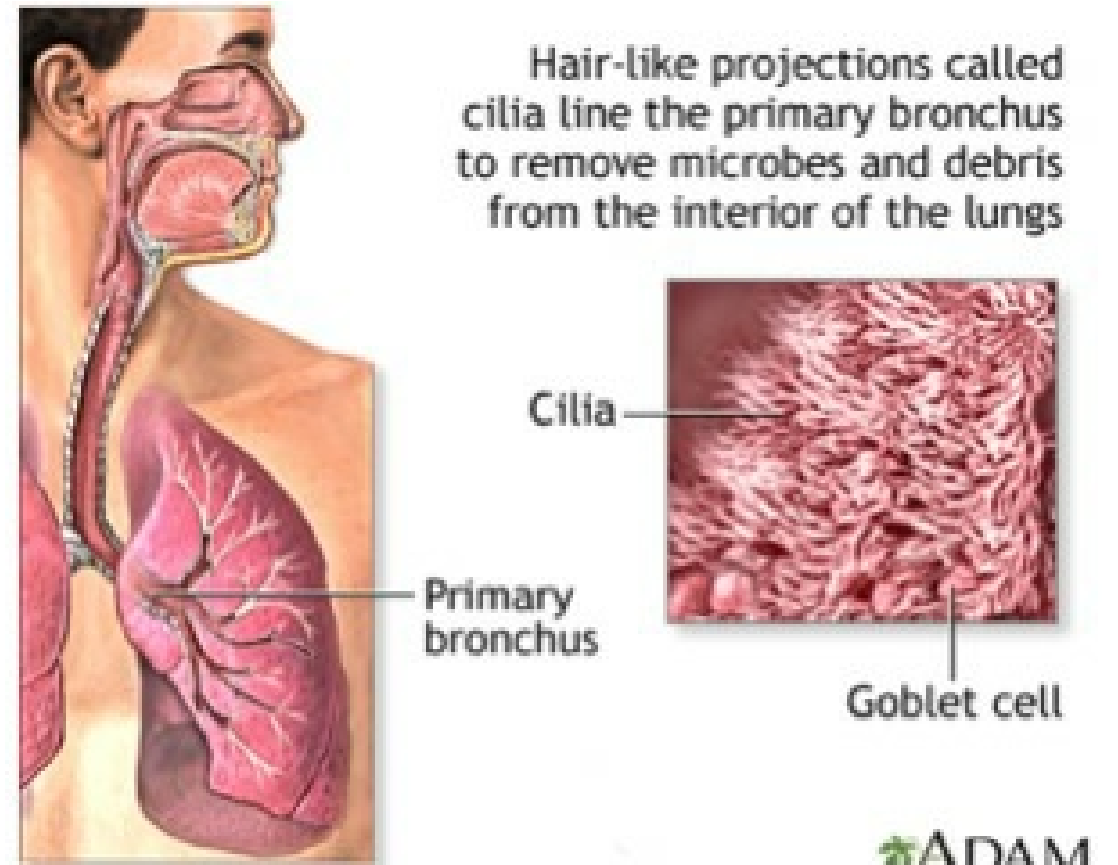


# Respiratory system

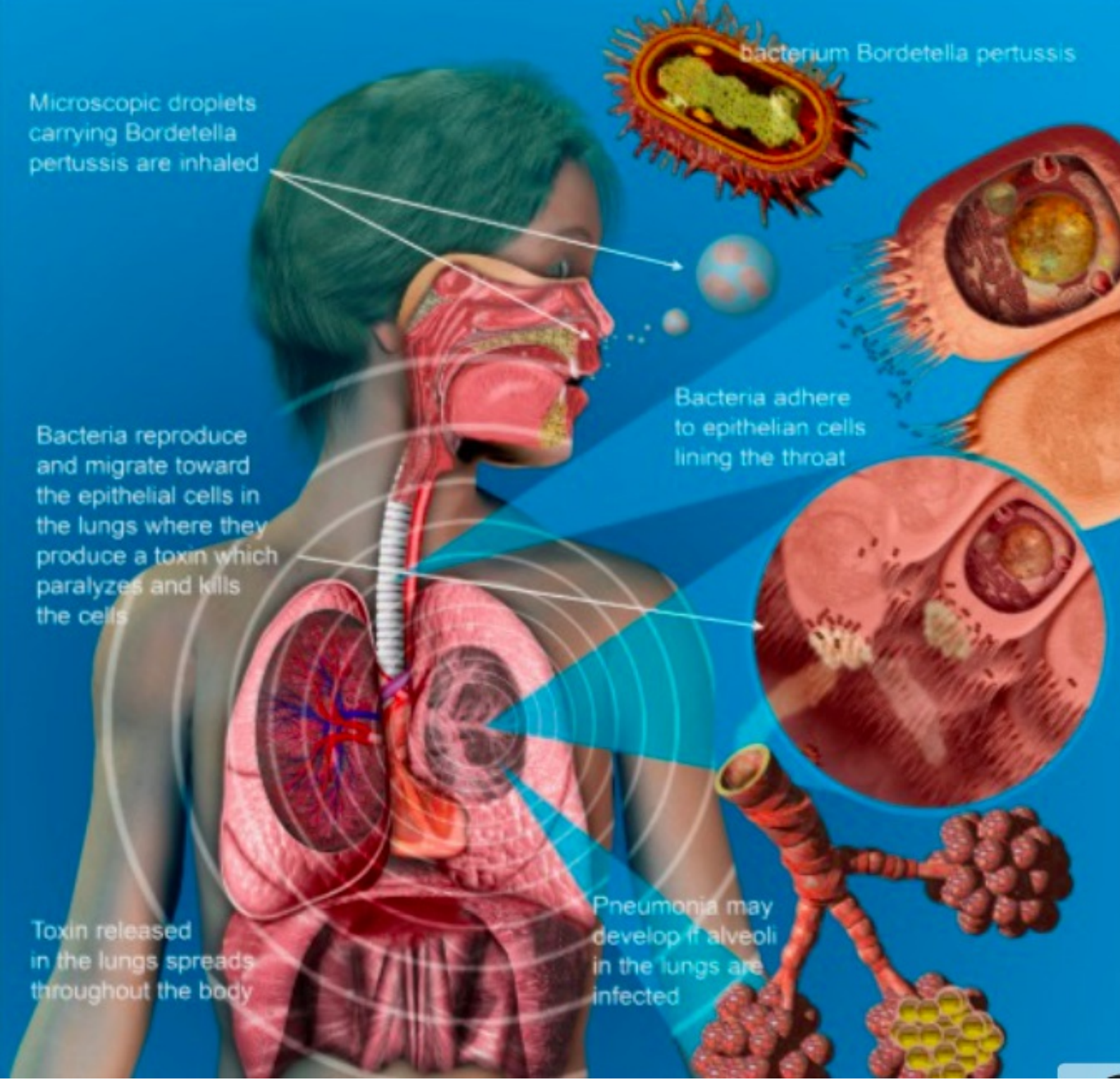
Involved with respiration/gas exchange, filtration, immune defense, phonation, olfaction, and humidification processes (via blood vessels along epithelial linings of the respiratory system).

## Goblet cells

- Line respiratory cell epithelial lining and secrete mucin, which combines with water to yield mucus
- Mucus acts in a defensive/protective manner by moistening the airways of the respiratory system
- Clearance of infectious particles







The inability to respire properly limits oxygen intake/carbon dioxide expulsion needed for normal physiological functions.

- *Bordetella pertussis* enters alveolar macrophages, which normally clear air spaces of the respiratory system.
- Entrance into alveolar macrophages induces phagocytosis within them, altogether reducing typical respiratory system innate immune defensive functions/airspace surveillance.
- Overall, tissue damage disturbs physiological functioning

# Disturbances to normal physiological functioning, caused by toxins:

## Tracheal Cytotoxin

1. Paralyzes the cilia of ciliated cells of the respiratory system, which yields loss of cilia sweeping function.
2. The normal sweeping function of cilia move mucus and bacteria along the airways, acting as a defensive barrier preventing pathogenic penetration, damage, and/or bacterial colonization of the respiratory epithelial lining.
3. Paralysis of the cilia permits pertussis adherence & mucus build up, which triggers violent persistent coughing, choking and sometimes vomiting.



**Destruction and paralysis of the cilia**

- Prevent normal foreign particle/pathogen clearance functions

Normal functioning of the circulatory system is also affected:

**Bordetella Pertussis produces heat-labile toxin, which yields strong vasoconstrictive effects in the blood causing increased blood pressure during the early phase of pertussis**



## Filamentous hemagglutinin, Pertactin, and Agglutinin.

Anchor pathogen to the respiratory epithelium, and allow it to attach and initiate damage against respiratory epithelial cells in a manner which diminishes cell function..

## Pertussis toxin

1. Pertussis yields increased T cell divisions. T cells exit the thymus and enter circulation. When reach infectious sites however, pertussis toxin blocks them from leaving the blood/migrating into tissues to act, causing T cell build-up in the blood.
2. Makes the blood vessels and respiratory system more sensitive to histamine, causing fluid to seep into the airway tissues,
3. Increased fluid causes airway swelling making breathing difficult and yields the characteristic "whooping."



**Bacterial toxins induce lymphocytosis**

**Increased lymphocytes in blood above what is normal — due to T cell differentiation and tissue migration blockage by pertussis toxin**

## Adenylate cyclase

1. Blocks phagocytes from getting to the site of infection and prevents bacterial killing once the macrophages engulf the pathogen.
2. Induces host phagocyte apoptosis atypical from resting uninfected states



The main preventative measure for Bordetella pertussis infection is:

## Administration of the DaTP vaccine.

However, in this case our patient displayed clinical symptoms and no history of recent vaccinations thus, became susceptible.

The recommended antimicrobial agents used for treatment are:

- [Azithromycin](#)
- [Clarithromycin](#)
- [Erythromycin](#)

These antibiotics fall under the family of **macrolides**

Works by Inhibiting protein synthesis within the bacterium by reversibly binding to the P site of the 50S subunit on its ribosome, **stopping translation**

This inhibits bacterial growth, and controls infection progression

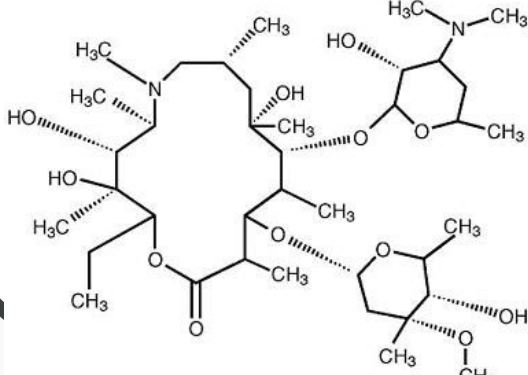
Patients that acquire pertussis at a younger age....

Azithromycin is the preferred treatment as it is not associated with infantile hypertrophic pyloric stenosis (near to complete obstruction of gastric outlet).

\* Treatment is recommended in a 14-day regime

1

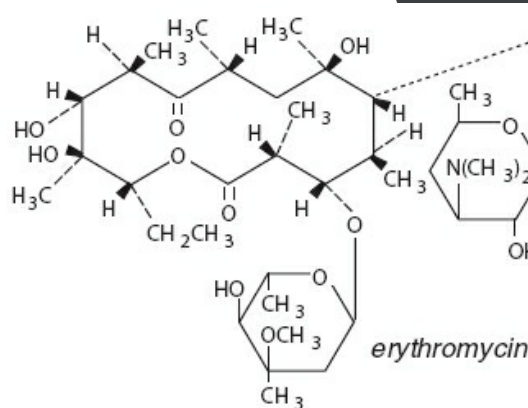
### Azithromycin:



- Azithromycin binds and inhibits erythromycin-strains (12).
- Targets Acyl-homoserine lactones (AHLs) by inhibiting LasR-dependent gene expression
- Inhibits biofilm expression
- Able to reach higher intracellular concentrations than erythromycin, thus increasing its efficacy and duration of action

2

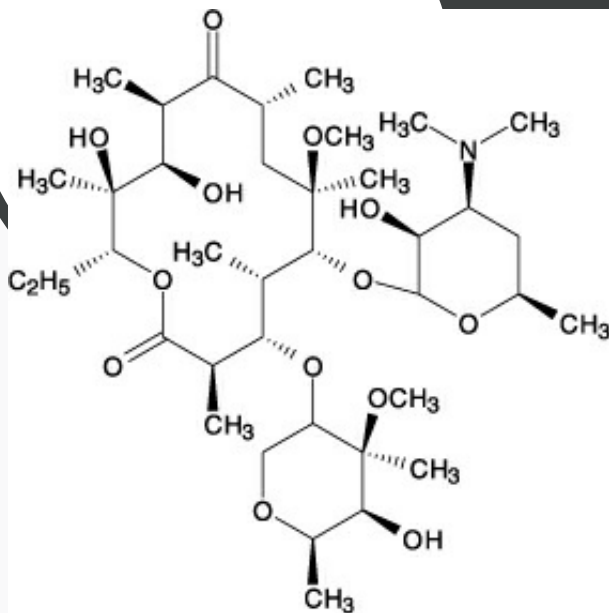
### Erythromycin:



- A macrolide antibiotic for treatment of upper respiratory tract and skin/soft tissue infections
- Binds to domain V of 23S ribosomal RNA of the 50s subunit of the bacterial ribosome inhibiting RNA-dependent protein synthesis
- Gastrointestinal intolerance and a short serum half-life have made this drug a less favourable antibiotic.

3

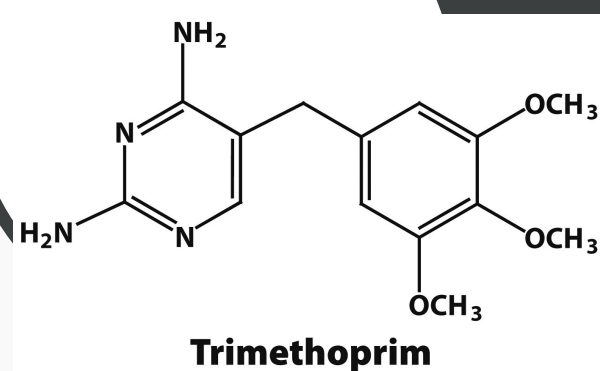
### Clarithromycin:



- Semisynthetic macrolide, differs from erythromycin in its methyl substitution at the number 6 position of the macrolide ring.
- Translocation of aminoacyl transfer-RNA and polypeptide synthesis is blocked by this antibiotic.
- Inhibits CYP3A4 enzyme and P-glycoprotein, which is an energy-dependent drug efflux pump.

4

### Trimethoprim:



- Binding to dihydrofolate reductase enzyme
- Inhibits the reduction of tetrahydrofolic acid (THF), starving the bacteria of nucleotides necessary for DNA replication.
- Affects the thymidine synthesis pathway
- Often combined with sulfamethoxazole as it displays synergistic effects

5

### Sulfamethoxazole:

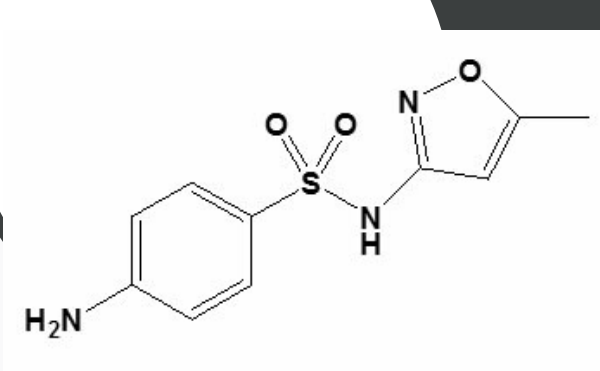


Fig. 1: Sulfamethazole (SZ) drug

- Sulphonamide drug
- Inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA) for the binding to dihydrofolate synthetase.

## References:

- Altunajji S, Kukuruzovic R, Curtis N, Massie J. 2007. Antibiotics for whooping cough (pertussis). *Cochrane database of systematic reviews* doi:10.1002/14651858.CD004404.pub3:CD004404.
- Ben-Joseph EP, ed. Whooping Cough (Pertussis). *KidsHealth*. <http://kidshealth.org/en/parents/whooping-cough.html>. Published February 2016. Accessed November 16, 2017.
- CDC. 2017. Pertussis (Whooping Cough). <https://www.cdc.gov/pertussis/about/signs-symptoms.html>. Accessed Nov. 13.
- Codeine. *DrugBank*.
- Finger H, von Koenig CHW. Bordetella. In: Baron S, editor. *Medical Microbiology*. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 31. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK7813/>
- Gillis TP. 2015. Chapter 93 - Mycobacterium leprae A2 - Tang, Yi-Wei, p 1655-1668. In Sussman M, Liu D, Poxton I, Schwartzman J (ed), *Molecular Medical Microbiology (Second Edition)* doi:<https://doi.org/10.1016/B978-0-12-397169-2.00093-7>. Academic Press, Boston.
- Gualerzi CO. 2013. Wiley-VCH.
- How does whooping cough (pertussis) affect the body? | Whooping Cough. *Sharecare*.
- Konkel L. 2017. Pertussis in Adults. <https://www.healthline.com/health/new-baby-vaccination-guide/pertussis-in-adults-signs-symptoms#overview1>. Accessed Nov. 14.
- List of Macrolides. *Drugs.com*. <https://www.drugs.com/drug-class/macrolides.html>. Accessed November 17, 2017.
- Mazzei T, Mini E, Novelli A, Periti P. 2010. *ChemInform Abstract: Chemistry and Mode of Action of Macrolides*. *ChemInform* 24.
- McMullan BJ, Mostaghim M. Prescribing azithromycin. *Australian Prescriber*. 2015;38(3):87-89. doi:10.18773/austprescr.2015.030.
- Mucociliary Escalator. *Biological Sciences Initiative*. University of Colorado at Boulder.
- Overview of the Respiratory System - Lung and Airway Disorders. *Merck Manuals Consumer Version*
2017. Pertussis (whooping cough) - causes, symptoms, diagnosis, treatment, pathology. *YouTube*. *YouTube*.
- Pertussis. *WHO*. <http://www.who.int/immunization/diseases/pertussis/en/>. Accessed November 16, 2017
- PhD CPDMD. Is Whooping Cough (Pertussis) Contagious? *MedicineNet*.
- WI KTM. *Online Textbook of Bacteriology*. *Online Textbook of Bacteriology*.
- Pertussis (Whooping Cough). *Centers for Disease Control and Prevention*. <https://www.cdc.gov/pertussis/about/signs-symptoms.html>. Published August 7, 2017. Accessed November 17, 2017.
- Stöppler MDMC. Whooping Cough Treatment, Sound, Symptoms & Pertussis Vaccine. *MedicineNet*. <https://www.medicinenet.com/pertussis/article.htm>. Accessed November 17, 2017.
- Wilson R, Read R, Thomas M, et al. Effects of Bordetella pertussis infection on human respiratory epithelium in vivo and in vitro. *Infection and Immunity*. 1991;59(1):337-345.
- Whooping cough. *Encyclopedia of Children's Health*. <http://www.healthofchildren.com/U-Z/Whooping-Cough.html>. Accessed November 16, 2017.
- Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, Assempour N, Iynkkaran I, Liu Y, Maciejewski A, Gale N, Wilson A, Chin L, Cummings R, Le D, Pon A, Knox C, Wilson M. 2017. *DrugBank 5.0: a major update to the DrugBank database for 2018*. *Nucleic Acids Res* doi:10.1093/nar/gkx1037.
- Zuckerman JM, Qamar F, Bono BR. 2009. Macrolides, ketolides, and glycolcyclines: azithromycin, clarithromycin, telithromycin, tigecycline. *Infect Dis Clin North Am* 23:997-1026, ix-x.