PÉCSI TUDOMÁNYEGYETEM
ÁLTALÁNOS ORVOSTUDOMÁNYI KAR
Immunológiai és Biotechnológiai Intézet

Biotechnology 2018

Biological therapies

Vaccines against bacteria and parasites

Najbauer József

Lectures 19-20; 2018. 04. 12.

Lecture outline

1. Introduction

2. Significant bacterial pathogens

3. (The immune system – Key definitions)

4. Bacterial diseases and vaccines

5. Parasitic diseases and vaccines

6. Conventional vaccinology and vaccinology in the genome era

The fathers of immunology and vaccinology

Kaufmann SHE, Nature Rev Microbiol, 2007

(**a**) Edward Jenner (1749–1823), (**b**) Louis Pasteur (1822–1895), (**c**) Paul Ehrlich (1854–1915), (**d**) Emil Behring (1854–1917)

What have vaccines achieved so far?

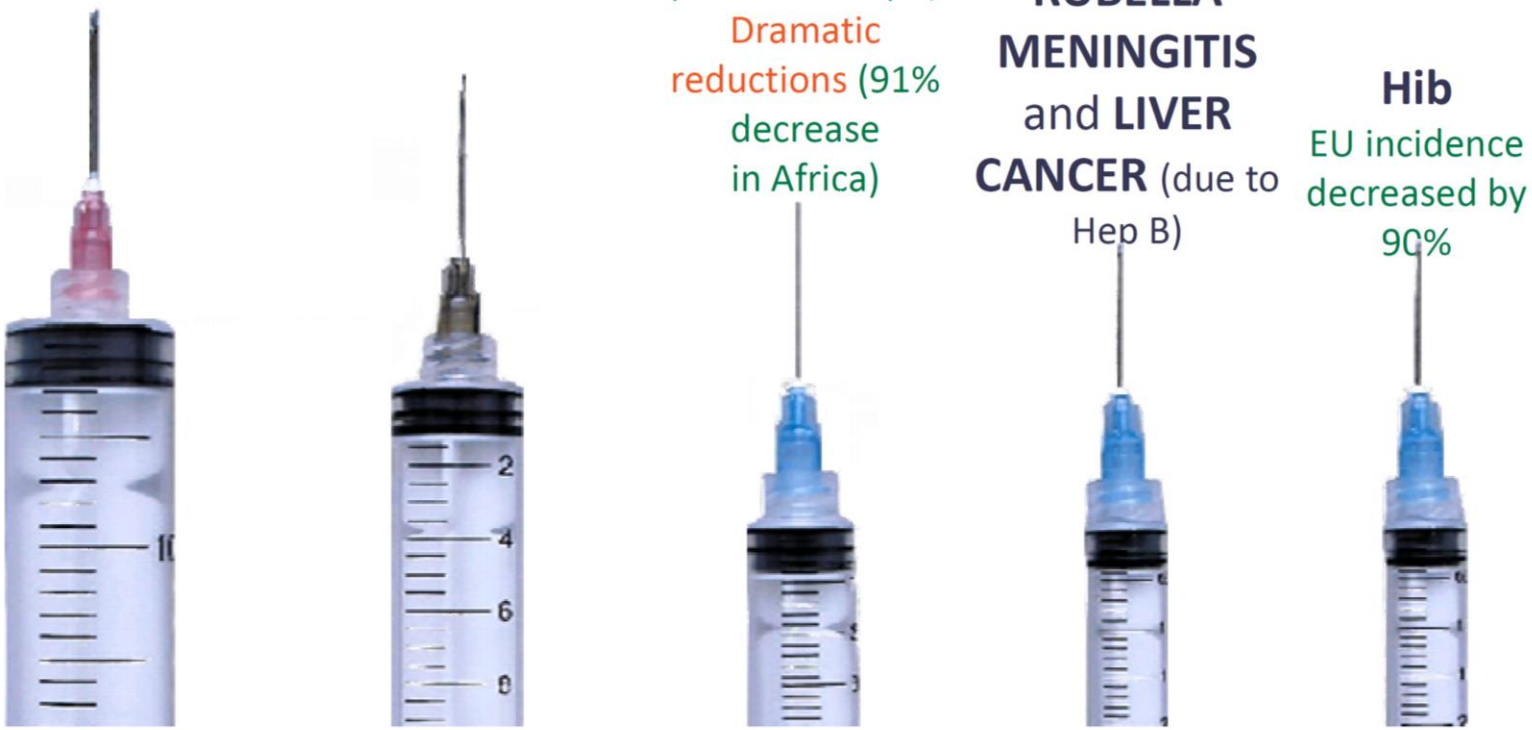
SMALLPOX
Eradicated in 1980

POLIO
Worldwide incidence decreased by 99%

MEASLES
Controlled (the Americas and parts of Europe)
Dramatic reductions (91% decrease in Africa)

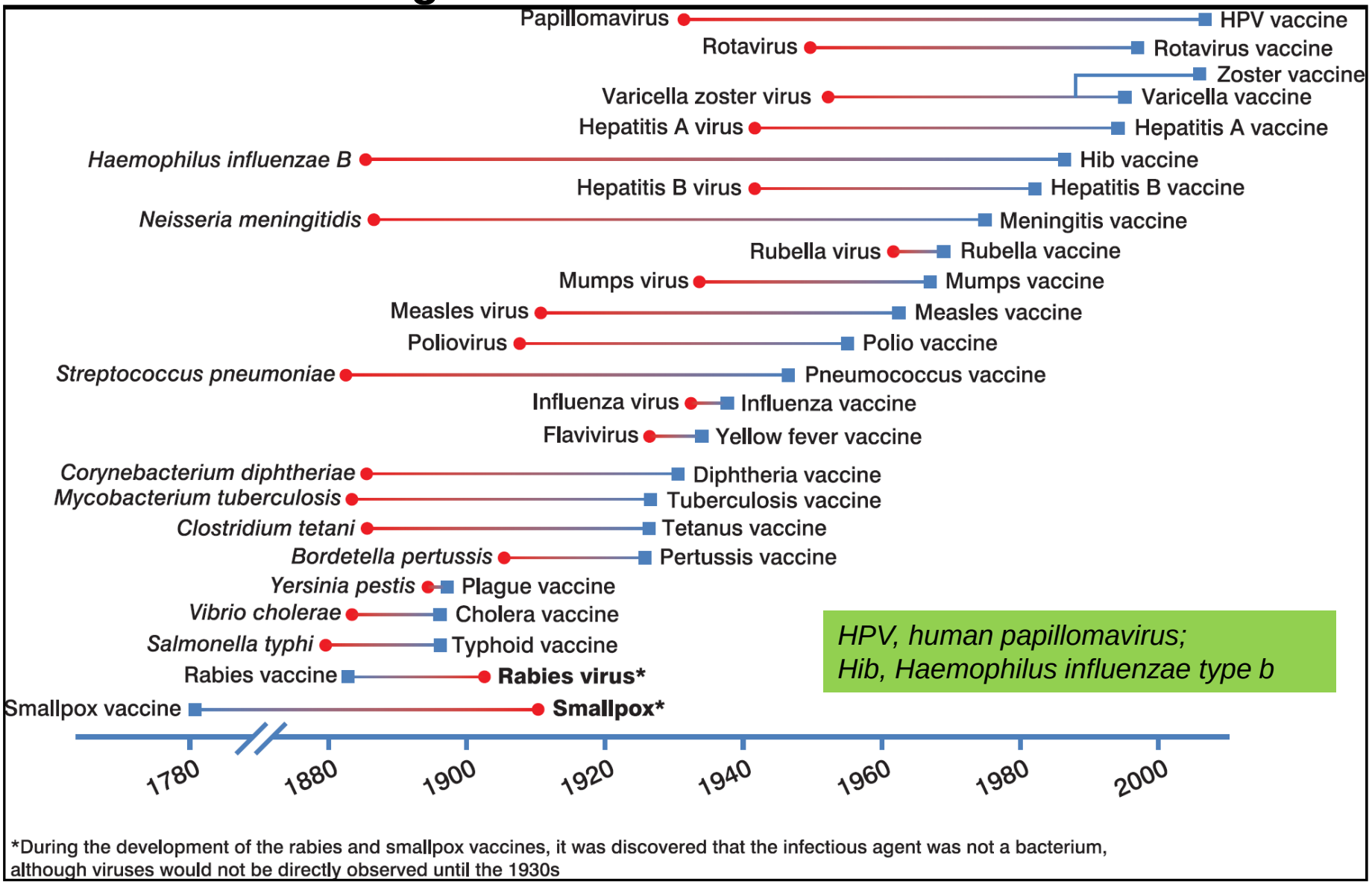
TETANUS
DIPHTHERIA
RUBELLA
MENINGITIS
and **LIVER CANCER** (due to Hep B)

Hib
EU incidence decreased by 90%



http://www.agah.eu/fileadmin/_migrated/content_uploads/Peeters__Mathieu_-_Joint_Conference_of_European_Human_Pharmacological_Societies_Berlin_March_2011_Final_version.pdf

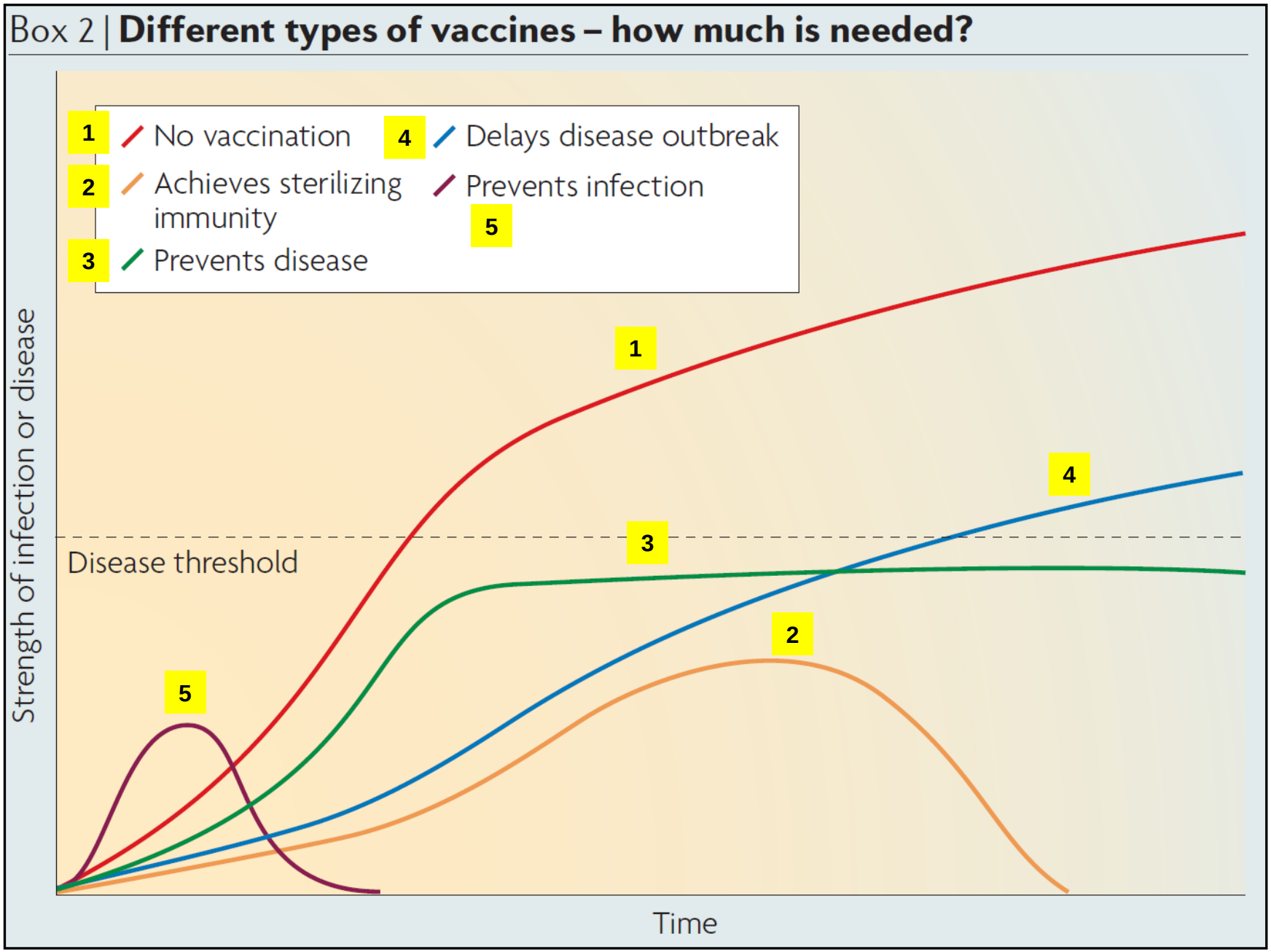
Pathogen isolation and vaccines



Bonanni & Ignacio Santos, Perspectives Vaccinol, 2011

Depending on availability of appropriate technology, there may be considerable variations in time between pathogen identification ● and development of a vaccine ■. In the case of smallpox, a vaccine was available long before viruses as causing agents were known. The rabies vaccine was also developed before knowing the causative agent. A pathogen, like varicella zoster virus, may cause different diseases (varicella and zoster) for which separate vaccines have been developed.

Possible outcomes of infection in vaccinated individuals



Immunization schedule in Hungary

World Health Organization

Return to the schedule selection centre form

WHO vaccine-preventable diseases: monitoring system. 2014 global summary

Immunization schedule for 66 vaccines (BCG, CHOLERA, Dip, DT, DTaP, DTaPHepBIPV, DTaPHepIPV, DTaPHib, DTaPHibHep, DTaPHibHepB, DTaPHibHepIPV, DTaPHibIPV, DTaPIPV, DTIPV, DTP, DTPHibIPV, DTwP, DTwPHep, DTwPHib, DTwPHib, DTwPHibHep, DTwPHibHepB, DTwPHibIPV, DTwPIPV, HepA, HepAHepB, HepB, HFRS, HIB, HIB, HibMenC, HPV, Influenza, IPV, JapEnc, Measles, MenA, MenAC, MenACW, MenACWY, MenBC, MenC_conj, MM, MMR, MMRV, MR, Mumps, OPV, Pneumo_conj, Pneumo_ps, Rabies, Rotavirus, Rubella, TBE, Td, Tdap, Tdap, TdaPIPV, TdIPV, TT, Typhoid, TyphoidHepA, Varicella, VitaminA, YF, Zoster)
For 1 country (HUN) and for no specific region. 6 rows.

Country	Antigens	Description	Schedules	Entire country	Comments
		Europe			
Hungary	BCG	Bacille Calmette-Guérin vaccine	birth;	Yes	
	MMR	Measles mumps and rubella vaccine	15 months; 11 years;	Yes	
	HepB	Hepatitis B vaccine	13 years;	Yes	
	Pneumo_conj	Pneumococcal conjugate vaccine	2, 4, 15 months;	Yes	
	DTaPHibIPV	Diphtheria and tetanus toxoid with acellular pertussis, Hib and IPV vaccine	2, 3, 4, 18 months;	Yes	
	Tdap	Tetanus and diphtheria toxoids and acellular pertussis vaccine	11 years;	Yes	

Unless otherwise specified, data provided by Member States through WHO-UNICEF Joint Reporting Form and WHO Regional offices.

http://apps.who.int/immunization_monitoring/globalsummary/schedules

Some infections for which effective vaccines are not yet available

Some infections for which effective vaccines are not yet available	
Disease	**Estimated annual mortality**
Malaria	889,000
Schistosomiasis	41,000
Intestinal worm infestation	6,000
Tuberculosis	1.5 million
Diarrheal disease	2.2 million
Respiratory infections	4 million
HIV/AIDS	2 million
Measles†	400,000

Figure 16.22 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Significat bacterial pathogens

Streptococcus pneumoniae

Kaufmann SHE, Nature Rev Microbiol, 2007

- *Streptococcus pneumoniae* mostly afflicts the youngest (<2 years) and the oldest (>65 years) among us.

- Up to 1 million children worldwide die of pneumococcal disease each year and, in developing countries, 10–20% of all deaths among children are caused by pneumococci.

- Pneumococci cause bacterial pneumonia and influenza-like symptoms as well as otitis media, bacteraemia, sepsis and meningitis. Pneumococci are encapsulated and the carbohydrate components of the capsule are targets of protective immunity.

- Conjugate vaccines are already available, which cover a profound proportion of the 90 different pneumococcal serotypes that exist. These vaccines have achieved massive reduction of pneumococcal diseases; they also reduced pneumococcal colonization in vaccinated children and, consequently, the rate of transmission to non-vaccinated individuals of all ages. This reduction includes antibiotic-resistant strains. Hence, vaccination will increase the success rates of chemotherapy in the long term.

Neisseria meningitidis

- This commensal bacterium is found in up to 10% of the human population, who serve as asymptomatic carriers.

- Thirteen meningococcal serotypes have been identified, five of which are responsible for 90% of meningococcal diseases — meningitis and septicaemia.

- Worst hit are countries of the so-called meningitis belt in central Africa where epidemics strike periodically, the last one in 1996/1997, which afflicted more than 200,000 people.

- In 2007, a new epidemic seems to be on the rise and has already afflicted more than 22,000 people in Burkina Faso alone, with a 7% fatality rate. A vaccine that covers approximately half of all meningococcal diseases is already available.

Kaufmann SHE, Nature Rev Microbiol, 2007

Group A streptococci

- The typical purulent pathogens group A streptococci (*Streptococcus pyogenes*) cause different types of disease, which range from laryngitis/pharyngitis to invasive generalized disease.

- Group A streptococci colonize the upper respiratory tract in 10% of all individuals as commensals, from where they can spread to immunocompromised patients or invade diverse tissue sites.

- In the United States alone, 10 million new cases occur annually, most of them mild, but 10,000 of these cases take severe forms that have a 20% mortality rate.

Group B streptococci

- Serious invasive disease can be caused by group B streptococci (*Streptococcus agalactiae*) when newborns are infected during birth — typically by commensal streptococci from their mothers (puerperal fever).

- Group B streptococci are normal inhabitants of the vagina of up to one quarter of women in many parts of the world. Transmission of group B streptococci to newborns during labour and delivery is therefore a frequent event.

Kaufmann SHE, Nature Rev Microbiol, 2007

The major nosocomial pathogens

- *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae* represent the major nosocomial pathogens. They cause various diseases depending on the site of invasion, including pneumonia, urinary-tract infections and systemic infections, as well as skin and diverse tissue infections.

- Although these microorganisms can be treated by chemotherapy, there has been a dramatic increase in the incidence of multidrug-resistant strains; in particular meticillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Vancomycin is the last active drug available for the treatment of MRSA. However, vancomycin treatment favours VRE, and strains of vancomycin-resistant MRSA have already been identified.

- Some strains of *S. aureus* produce a multitude of toxins, including the toxic-shock-syndrome toxin that is responsible for the shock syndromes associated with menses and the enterotoxins that are responsible for major food poisoning. Enterotoxins and toxic-shock-syndrome toxin are superantigens, which can cause a cytokine storm or septic-shock-like syndrome.

Nosocomial (*adj*) - (of a disease) originating in a hospital

Kaufmann SHE, Nature Rev Microbiol, 2007

Mycobacterium tuberculosis

- *Mycobacterium tuberculosis* is a member of the infamous triad of killer pathogens that comprises the infective agents responsible for AIDS, malaria and tuberculosis (TB).

- Although we have a vaccine available (bacillus Calmette–Guérin (BCG)) which prevents childhood TB, this vaccine is ineffective in preventing the major form of the disease, pulmonary TB, in adults.

- TB is on the rise in numerous countries, and the situation is becoming increasingly exacerbated for two reasons: first, the increasing numbers of multidrug-resistant (MDR-TB) and even extensively drug resistant (XDR-TB) strains; and second, the deadly coalition between TB and HIV/AIDS. This makes the need for a new vaccine against TB more urgent than ever before, but also raises new complications.

Kaufmann SHE, Nature Rev Microbiol, 2007

Chlamydia trachomatis

- Transmitted during sexual intercourse at a rate of 90 million times annually, two-thirds of *Chlamydia trachomatis* infections occur in developing countries.

- *C. trachomatis* not only causes inflammation but also serves as a cofactor for the transmission of HIV and human papilloma virus, which are responsible for AIDS and cervical cancer, respectively. Furthermore, in the long term, *C. trachomatis* infection can also cause infertility and chronic pelvic inflammation.

Kaufmann SHE, Nature Rev Microbiol, 2007

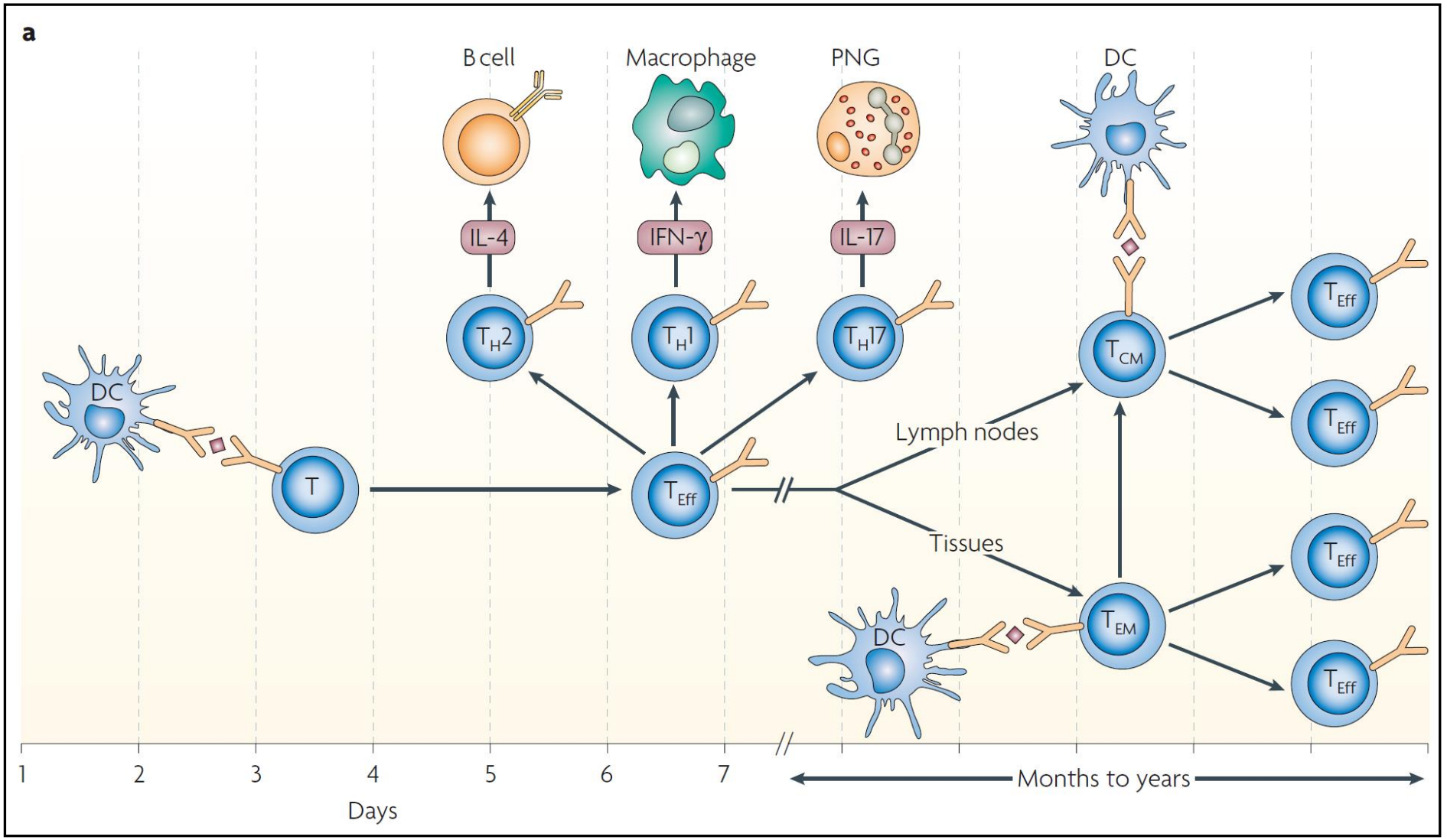
Helicobacter pylori

- The stomach-dwelling bacterium *Helicobacter pylori* has infected more than half of the world's population. It can remain silent, or it can cause gastroduodenal disease — notably peptic ulcers — which can later transform into stomach cancer. However, recent studies have proved that there is an inverse correlation between the presence of *H. pylori* in the stomach and oesophageal cancer, which indicates that there might be a protective role for *H. pylori* against this other lethal malignancy.

- Of course, the many bacterial pathogens that cause food-borne diseases — which, in most cases, result in diarrhoea — are of equal importance, but these pathogens are not covered here.

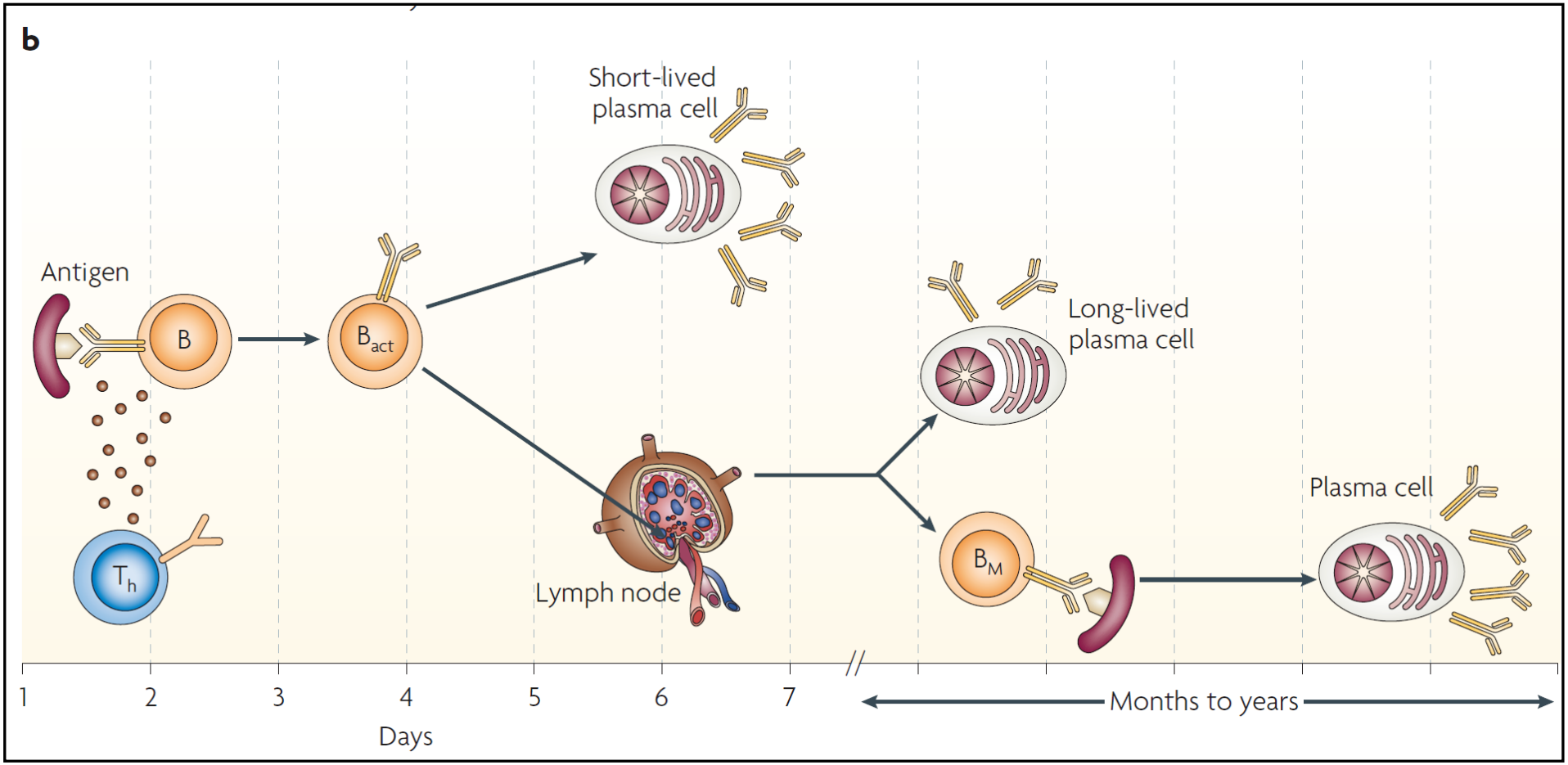
Kaufmann SHE, Nature Rev Microbiol, 2007

Memory generation in cells of the immune system: T cells



Kaufmann SHE, Nature Rev Microbiol, 2007

Memory generation in cells of the immune system: B cells



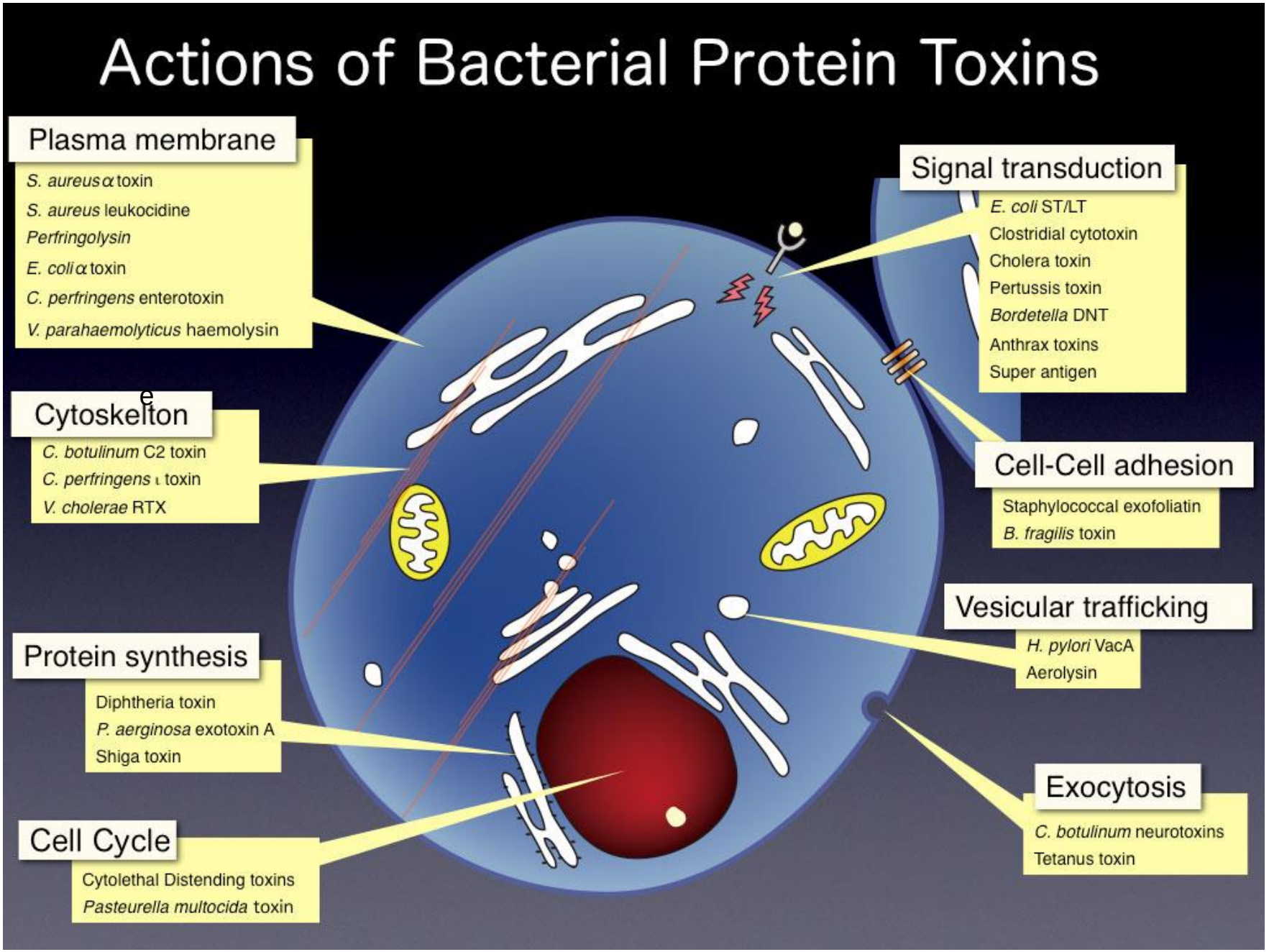
Kaufmann SHE, Nature Rev Microbiol, 2007

TABLE 15–2 Mechanisms of Immune Evasion by Bacteria

Mechanism of Immune Evasion	Examples
Extracellular bacteria	
Antigenic variation	*Neisseria gonorrhoeae, Escherichia coli, Salmonella typhimurium*
Inhibition of complement activation	Many bacteria
Resistance to phagocytosis	Pneumococcus
Scavenging of reactive oxygen species	Catalase-positive staphylococci
Intracellular bacteria	
Inhibition of phagolysosome formation	*Mycobacterium tuberculosis, Legionella pneumophila*
Inactivation of reactive oxygen and nitrogen species	*Mycobacterium leprae* (phenolic glycolipid)
Disruption of phagosome membrane, escape into cytoplasm	*Listeria monocytogenes* (hemolysin protein)

1

2



http://www.fbs.osaka-u.ac.jp/organelle-network/eng/research/18/

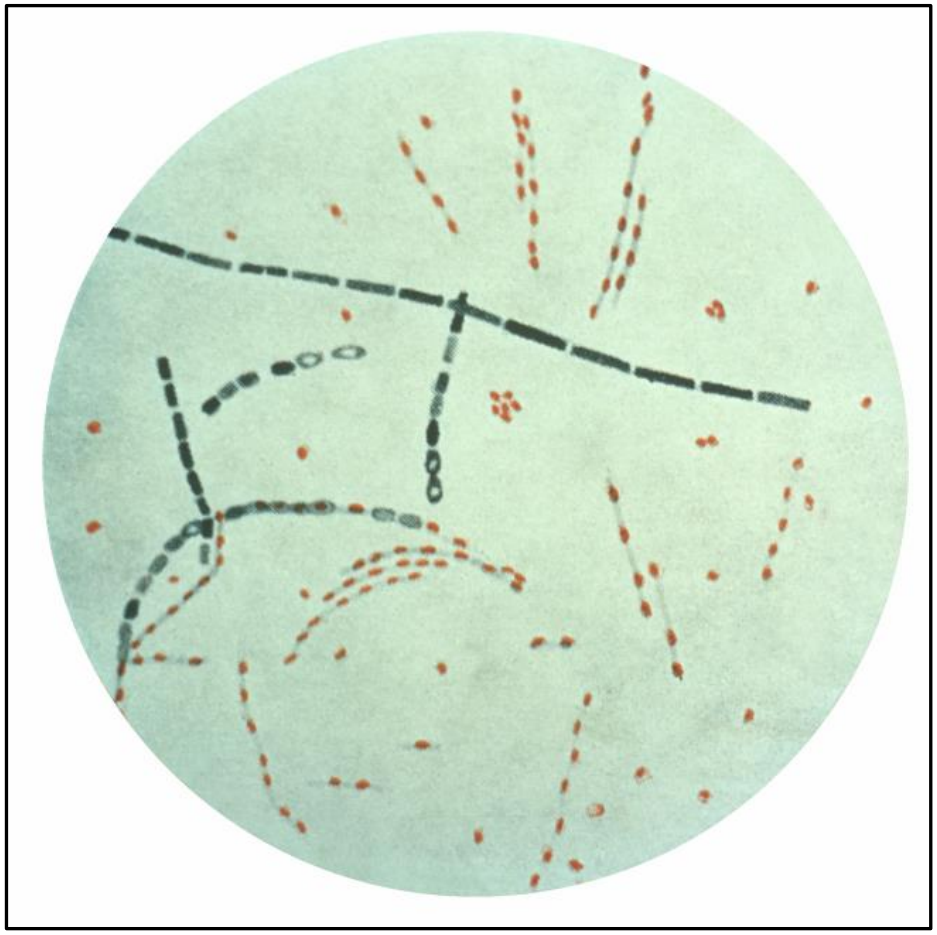
Bacterial diseases and vaccines

Bacterium	Diseases or conditions	Vaccine(s)	Brands
Bacillus anthracis 1	Anthrax	Anthrax vaccines	BioThrax
Bordetella pertussis 2	Whooping cough	DPT vaccine	Boostrix, Adacel, Daptacel, Infanrix, Tripedia, Kinrix, Pediarix, Pentacel
Clostridium tetani 3	Tetanus	DPT vaccine	Boostrix, Adacel, Decavac, Tenivac, Daptacel, Infanrix, Tripedia, Kinrix, Pediarix, Pentacel
Corynebacterium diphtheriae 4	Diphtheria	DPT vaccine	Boostrix, Adacel, Decavac, Tenivac, Daptacel, Infanrix, Tripedia, Kinrix, Pediarix, Pentacel
Coxiella burnetii 5	Q fever	Q fever vaccine	Q-Vax
Haemophilus influenzae type B (Hib) 6	Epiglottitis, meningitis, pneumonia	Hib vaccine	Hiberix, Pentacel, ActHIB, Pedvax HIB
Mycobacterium tuberculosis 7	Tuberculosis	Tuberculosis (BCG) vaccine	Tice BCG
Neisseria meningitidis 8	Meningococcal meningitis	Meningococcal vaccine	Neisvac C, Meningitec
Salmonella typhi 9	Typhoid fever	Typhoid vaccine	Typhim Vi, Typherix, Ty21a
Streptococcus pneumoniae 10	Pneumococcal pneumonia	Pneumococcal conjugate vaccine, Pneumococcal polysaccharide vaccine	Pneumovax, Prevnar
Vibrio cholerae 11	Cholera	Cholera vaccine	Dukoral, Shanchol

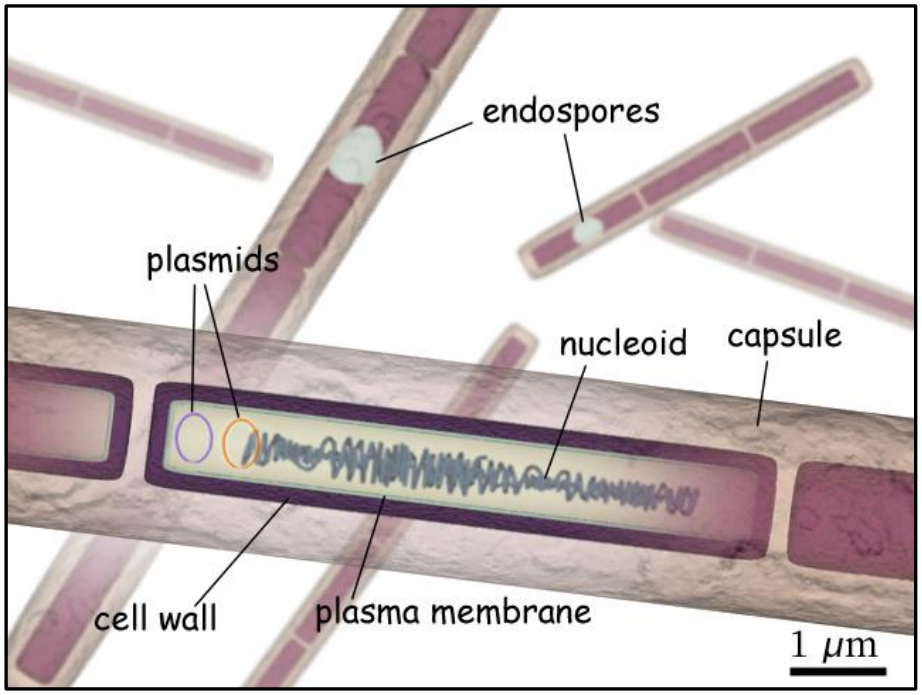
Wikipedia

Bacillus anthracis

Bacillus anthracis



Structure of *Bacillus anthracis*

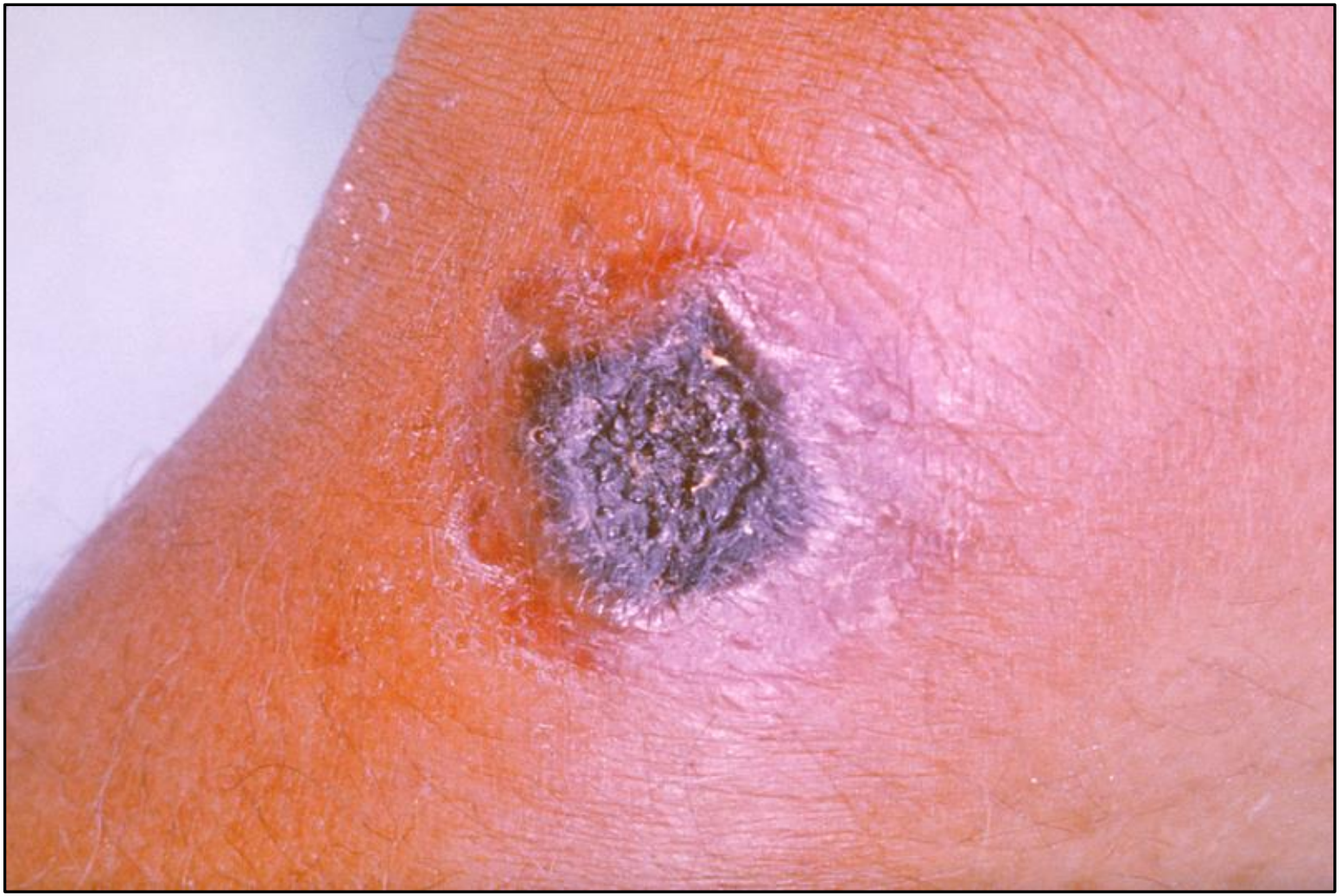


***Bacillus anthracis* from agar culture.**
Photomicrograph of *Bacillus anthracis* from an agar culture demonstrating spores; Fuchsin-methylene blue spore stain. Anthrax

http://phil.cdc.gov/phil/details.asp?pid=1792

www.wikipdia.org

Cutaneous anthrax



Anthrax is an acute disease caused by the bacterium *Bacillus anthracis*. Most forms of the disease are lethal, and it affects both humans and animals. There are effective vaccines against anthrax, and some forms of the disease respond well to antibiotic treatment

www.wikipdia.org

Anthrax

- **Cutaneous**

Cutaneous (on the skin) anthrax infection in humans presents as a boil-like skin lesion that eventually forms an ulcer with a black center (eschar).

- **Gastrointestinal**

Gastrointestinal infection in humans is most often caused by consuming anthrax-infected meat and is characterized by serious gastrointestinal difficulty, vomiting of blood, severe diarrhea, acute inflammation of the intestinal tract, and loss of appetite.

- **Pulmonary**

Respiratory infection in humans initially presents with cold or flu-like symptoms for several days, followed by pneumonia and severe (and often fatal) respiratory collapse.

Anthrax vaccine

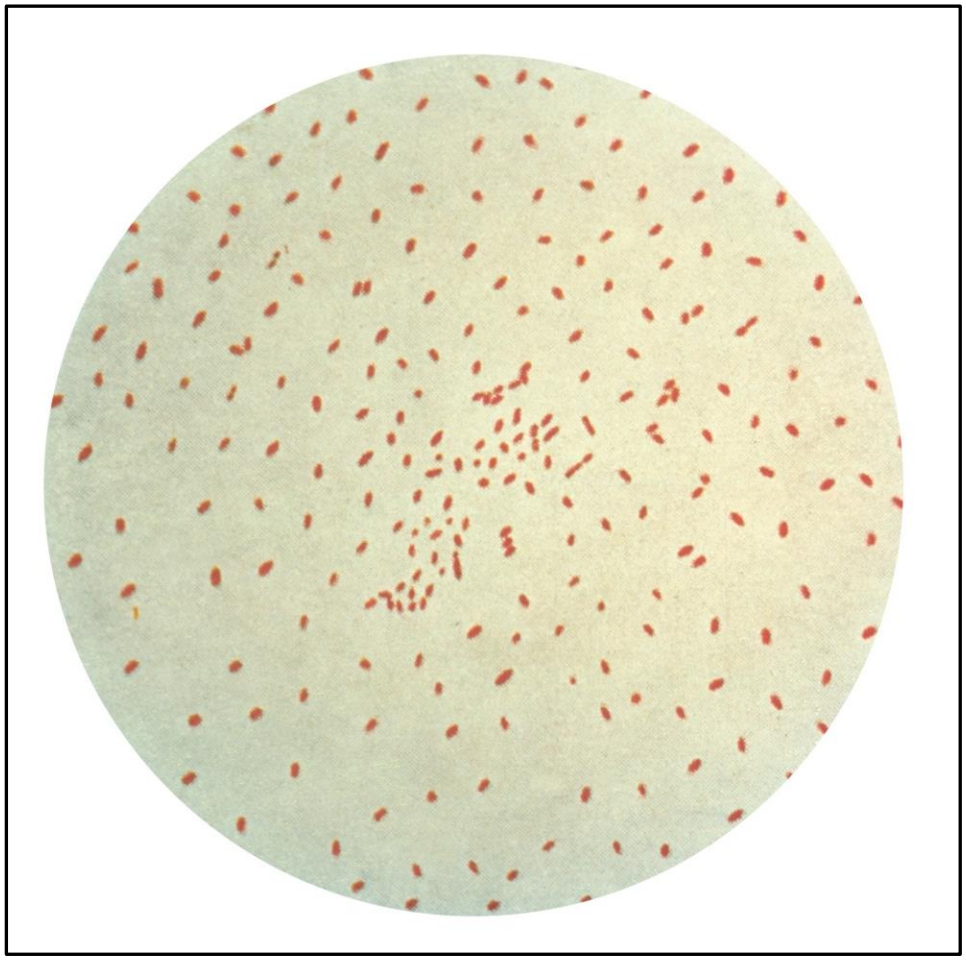
- Currently administered human anthrax vaccines include acellular (USA, UK) and live spore (Russia) varieties.

- All currently used anthrax vaccines show considerable local and general reactogenicity (erythema, induration, soreness, fever) and serious adverse reactions occur in about 1% of recipients.

- New second-generation vaccines currently being researched include recombinant live vaccines and recombinant subunit vaccines.

Bordetella pertussis

Bordetella pertussis is a Gram-negative, aerobic coccobacillus of the genus *Bordetella*, and the causative agent of pertussis or whooping cough.



http://phil.cdc.gov/phil/details.asp?pid=2121

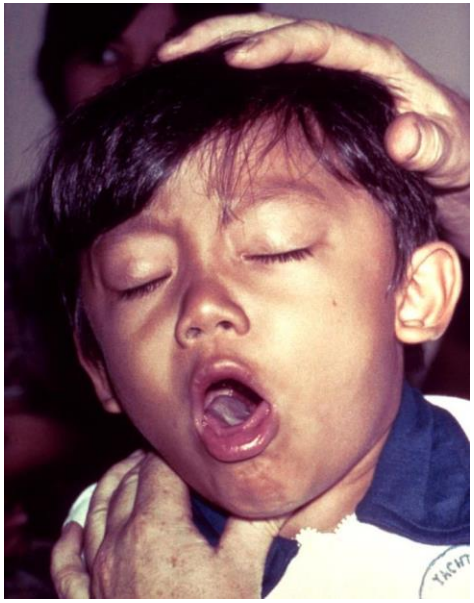
- This Gram-stained photomicrograph depicts numbers of *Bordetella pertussis* bacteria, which is the etiologic pathogen for pertussis, also known as whooping cough.
- A highly-communicable, vaccine-preventable disease that lasts for many weeks, pertussis typically manifests in children with paroxysmal spasms of severe coughing, whooping, and post-tussive vomiting, also known as Bordet-Gengou bacillus.
- Its virulence factors include pertussis toxin, filamentous hæmagglutinin, pertactin, fimbria, and tracheal cytotoxin.

Pertussis

Commonly called whooping cough — is a highly contagious bacterial disease caused by *Bordetella pertussis*. In some countries, this disease is called the 100 days' cough or cough of 100 days.

Symptoms are initially mild, and then develop into severe coughing fits, which produce the namesake high-pitched "whoop" sound in infected babies and children when they inhale air after coughing. The coughing stage lasts approximately six weeks before subsiding.

Prevention by vaccination is of primary importance given the seriousness of the disease in children. Although treatment is of little direct benefit to the person infected, antibiotics are recommended because they shorten the duration of infectiousness. It is currently estimated that the disease annually affects 48.5 million people worldwide, resulting in nearly 295,000 deaths.



A young boy coughing due to pertussis

Child with broken blood vessels in eyes and bruising on face due to pertussis coughing.

http://www.vaccineinformation.org/photos/pert_wi001.jpg

Who should get DTaP vaccine and when?

Children should get 5 doses of DTaP vaccine, one dose at each of the following ages:

- ✓2 months
- ✓4 months
- ✓6 months
- ✓15-18 months
- ✓4-6 years

DTaP may be given at the same time as other vaccines.

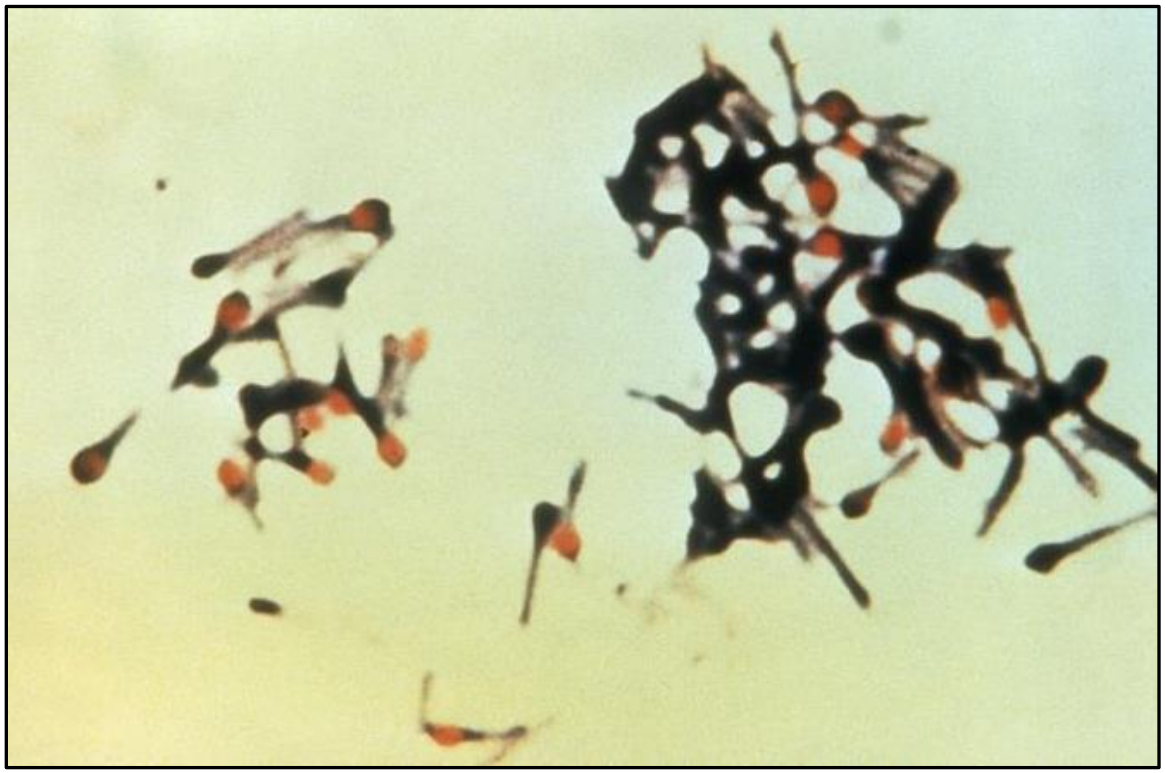
D – Diphtheria, T – Tetanus, P – Pertussis, 'a' - acellular

http://www.cdc.gov/pertussis/about/index.html

Clostridium tetani

- ***Clostridium tetani*** is an anaerobic bacterium of the genus species *Clostridium*. *C. tetani* is found as spores in soil.

- *C. tetani* produces a potent biological toxin, tetanospasmin, and is the causative agent of tetanus, a disease characterized by painful muscular spasms involving the jaw (lockjaw) and neck, then becoming generalized, which can lead to respiratory failure and, in up to 40% of cases, death.



Group of *Clostridium tetani* bacteria, responsible for causing tetanus in humans.

http://phil.cdc.gov/phil/details.asp?pid=6372

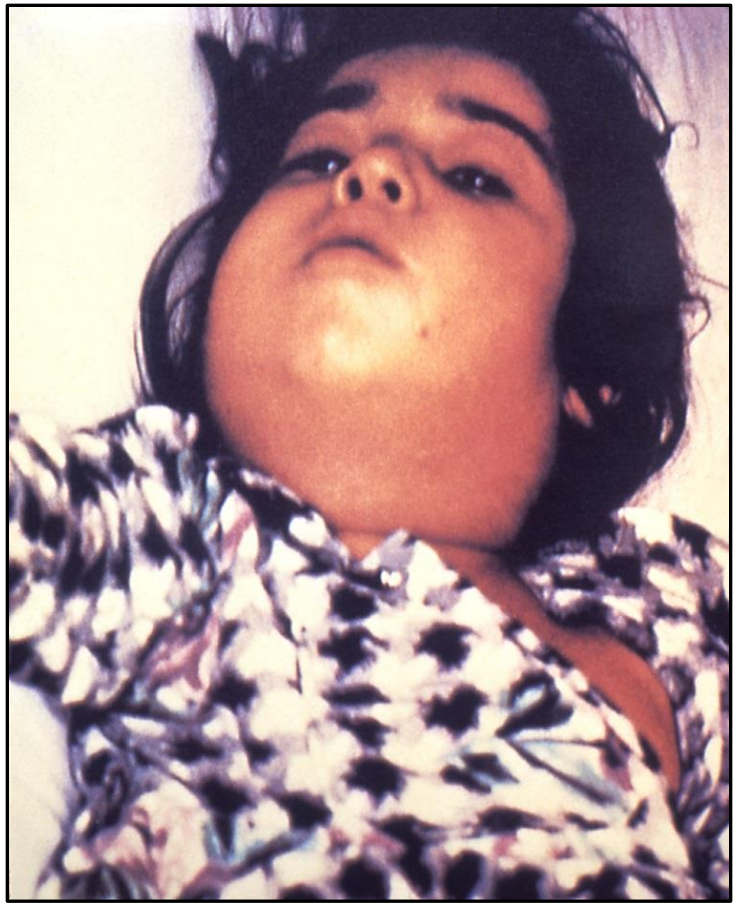
- **Tetanus** (from Ancient Greek: τέτανος *tetanos* “taut”, and τείνειν *teinein* "to stretch") is a medical condition characterized by a prolonged contraction of skeletal muscle fibers. The primary symptoms are caused by tetanospasmin, a neurotoxin produced by the Gram-positive, rod-shaped, obligate anaerobic bacterium *Clostridium tetani*.

- Infection generally occurs through wound contamination and often involves a cut or deep puncture wound. As the infection progresses, muscle spasms develop in the jaw (thus the name "lockjaw") and elsewhere in the body. Infection can be prevented by proper immunization or post-exposure prophylaxis.

Muscular spasms (specifically opisthotonous) in a patient suffering from tetanus. Painting by Sir Charles Bell, 1809.

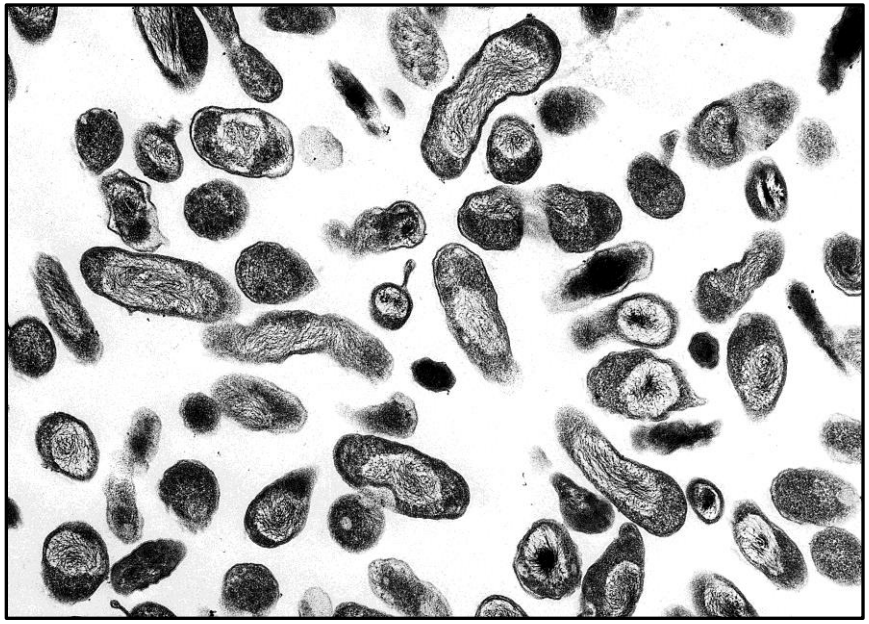
Opisthotonous - from Greek roots, *opistho* meaning ‘behind’ and *tonos* meaning ‘tension’.

Corynebacterium diphtheriae



Corynebacterium diphtheriae is a pathogenic bacterium that causes diphtheria. It is also known as the **Klebs-Löffler bacillus**, because it was discovered in 1884 by German bacteriologists Edwin Klebs (1834–1912) and Friedrich Löffler (1852–1915).

Coxiella burnetii

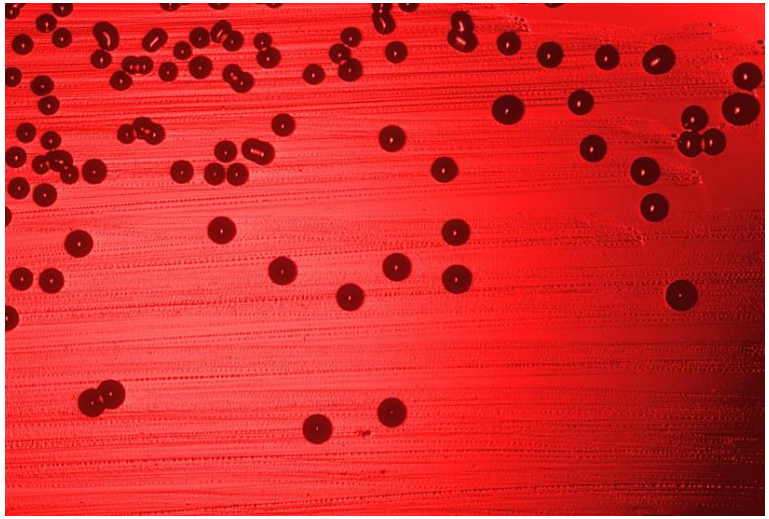


C. burnetii, the causative agent of Q fever

Coxiella burnetii is an obligate intracellular bacterial pathogen, and is the causative agent of **Q fever.**

C. burnetii is a small Gram-negative bacterium that is highly resistant to environmental stresses such as high temperature, osmotic pressure, and ultraviolet light. It can survive standard disinfectants, and is resistant to many other environmental changes like those presented in the phagolysosome.

Haemophilus influenzae

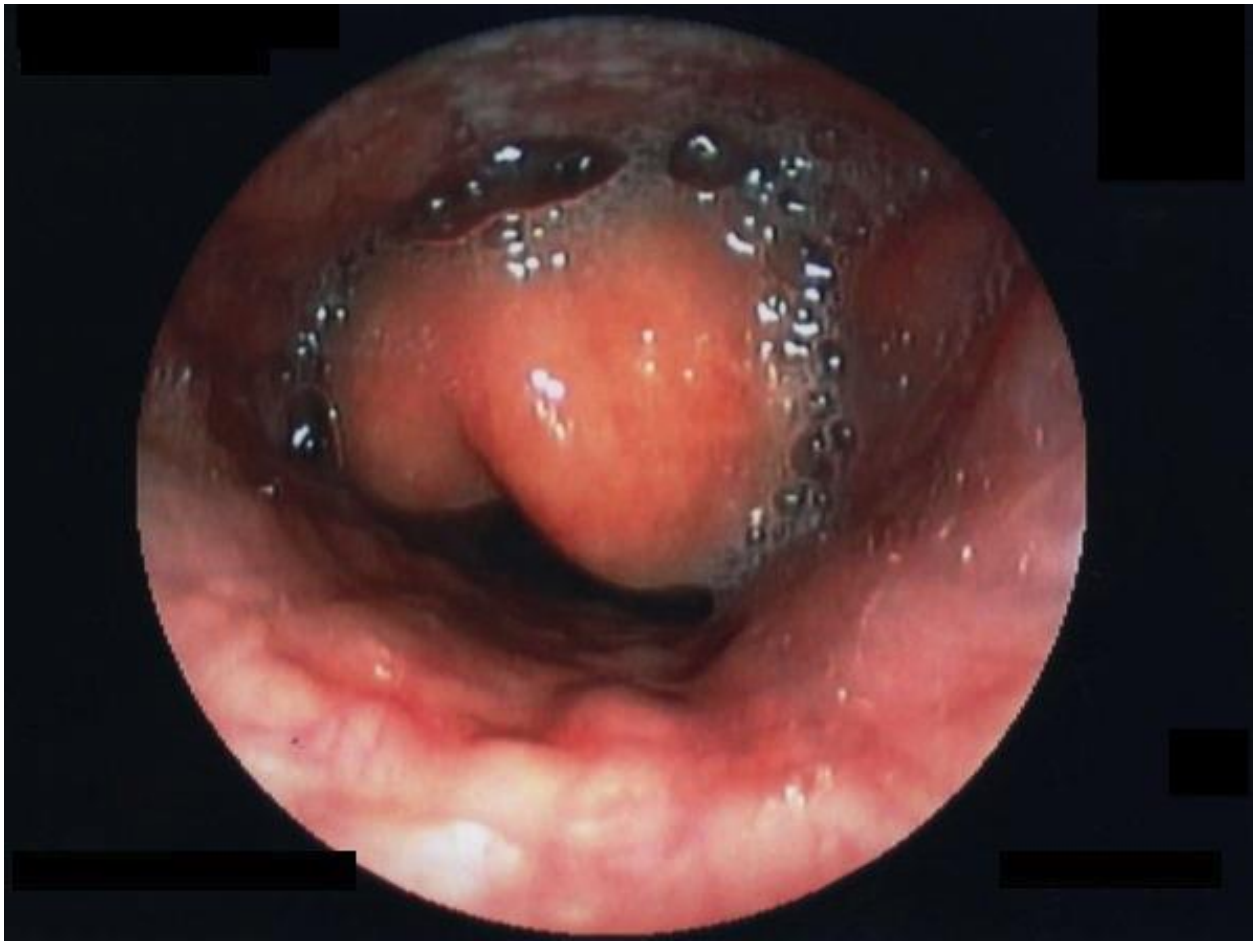


Haemophilus influenzae, formerly called **Pfeiffer's bacillus** or ***Bacillus influenzae***, is a Gram-negative, coccobacilli bacterium first described in 1892 by Richard Pfeiffer during an influenza pandemic. A member of the *Pasteurellaceae* family, it is generally aerobic, but can grow as a facultative anaerobe.

H. influenzae was mistakenly considered to be the cause of influenza until 1933, when the viral etiology of influenza became apparent.

The bacterium is colloquially known as *bacterial influenza*. Still, *H. influenzae* is responsible for a wide range of clinical diseases. *H. influenzae* was the first free-living organism to have its entire genome sequenced. The sequencing project was completed and published in 1995.

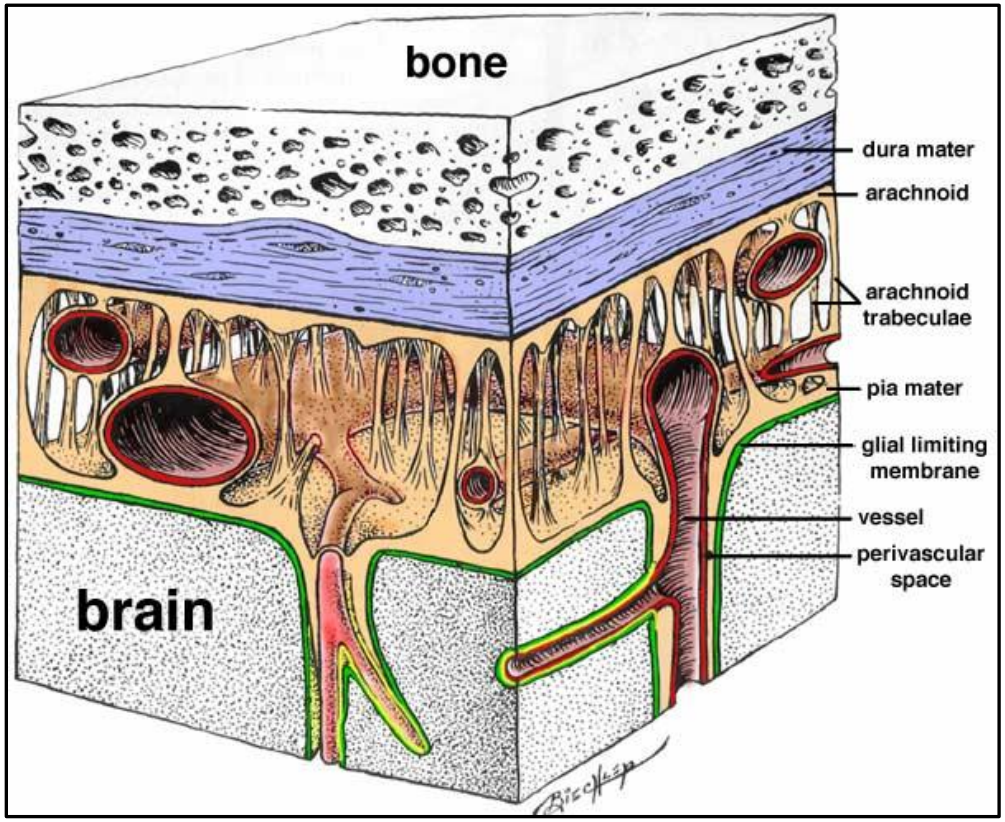
Epiglottitis



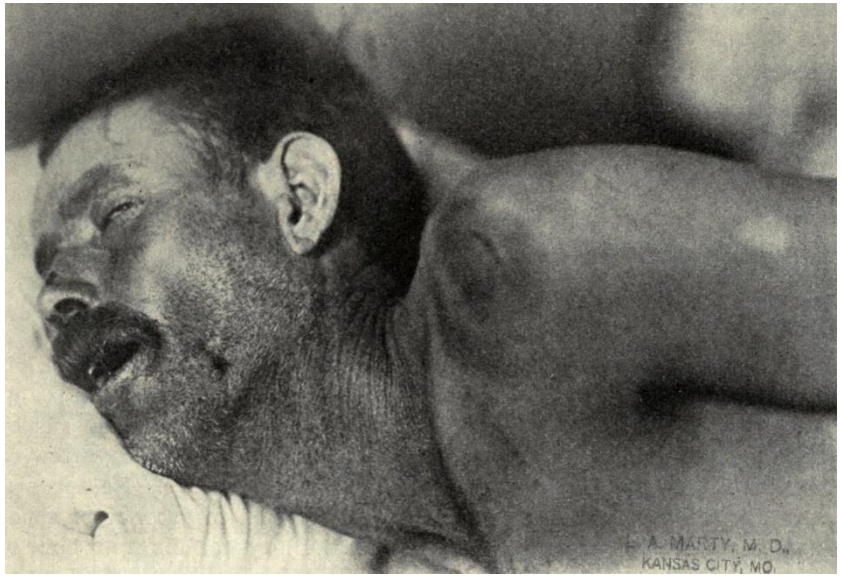
Epiglottitis is an inflammation of the epiglottis — the flap at the base of the tongue that keeps food from going into the trachea (windpipe). Due to its place in the airway, swelling of this structure can interfere with breathing, and constitutes a medical emergency. Infection can cause the epiglottis to obstruct or completely close off the windpipe. With the advent of the Hib vaccine, the incidence of epiglottitis has decreased, but the condition has not been eliminated.

Meningitis

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges. The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs. Meningitis can be life-threatening because of the inflammation's proximity to the brain and spinal cord; therefore, the condition is classified as a medical emergency.



http://vanat.cvm.umn.edu/neurHistAtls/pages/men1.html



Neck stiffness, Texas meningitis epidemic of 1911–1912.

- **Haemophilus influenzae type B vaccine** (Hib janan or PRP vaccine is a conjugate vaccine developed for the prevention of invasive disease caused by Haemophilus influenzae type b bacteria.

- The Centers for Disease Control and Prevention (CDC) has recommended the use of the Hib vaccine. Due to routine use of the Hib vaccine in the U.S. from 1980 to 1990, the incidence of invasive Hib disease has decreased from 40–100 per 100,000 children down to 1.3 per 100,000. Vaccinations against *Haemophilus influenzae* (Hib) have decreased early childhood meningitis significantly in developed countries and recently in developing countries.

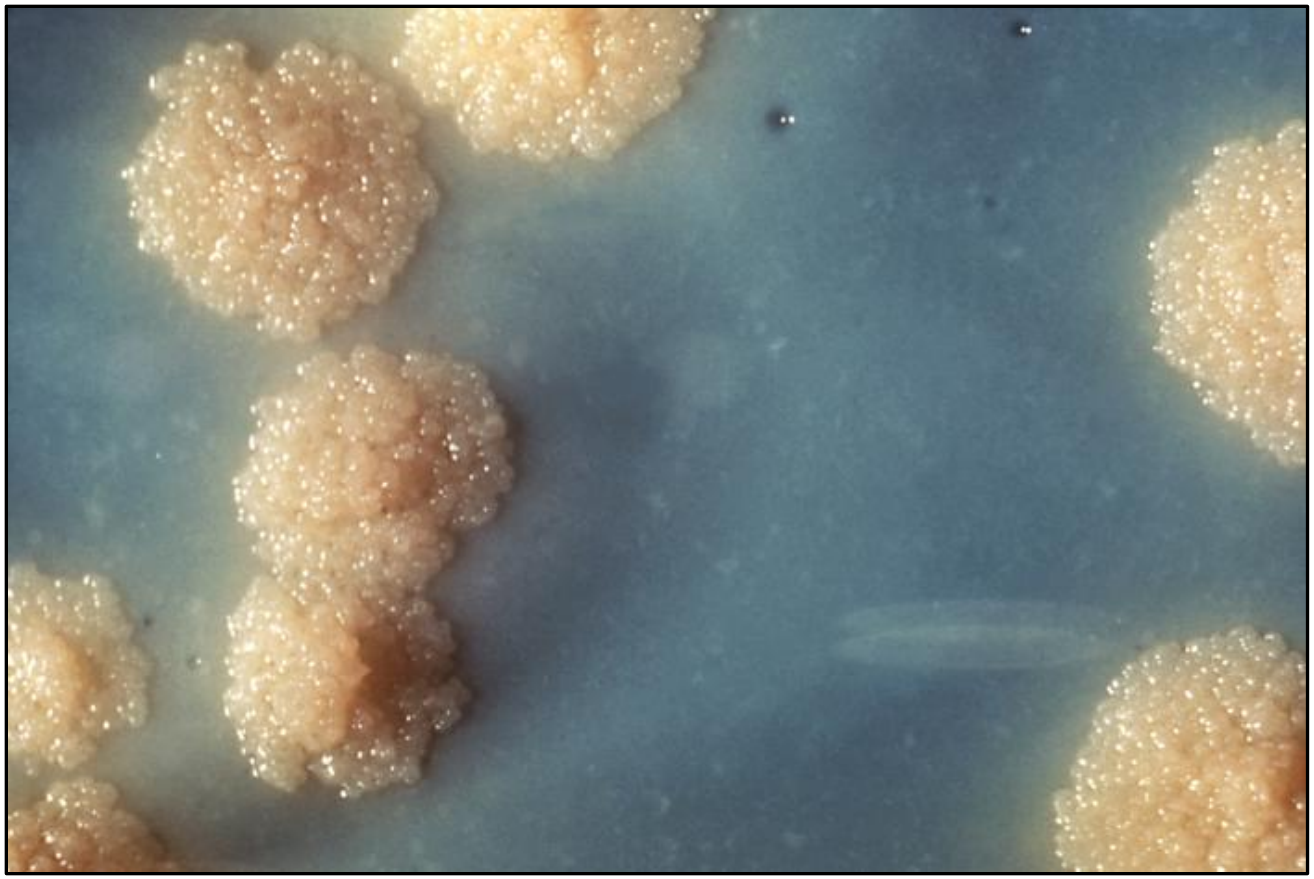
Mycobacterium tuberculosis

- ***Mycobacterium tuberculosis*** (MTB) is a pathogenic bacterial species in the family Mycobacteriaceae and the causative agent of most cases of tuberculosis (TB).

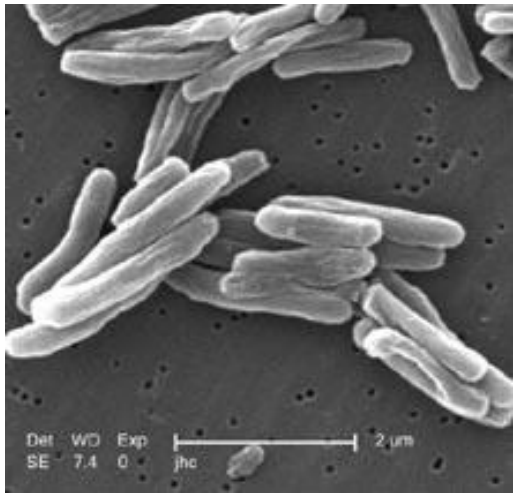
- First discovered in 1882 by Robert Koch, *M. tuberculosis* has an unusual, waxy coating on its cell surface (primarily mycolic acid), which makes the cells impervious to Gram staining. Acid-fast detection techniques are used instead. The physiology of *M. tuberculosis* is highly aerobic and requires high levels of oxygen.

- Primarily a pathogen of the mammalian respiratory system, MTB infects the lungs. The most frequently used diagnostic methods for TB are the tuberculin skin test, acid-fast stain, and chest radiographs. The *M. tuberculosis* genome was sequenced in 1998.

Mycobacterium tuberculosis (MTB) culture revealing this organism's colonial morphology. Note the colorless rough surface, which are typical morphologic characteristics seen in MTB colonial growth. Macroscopic examination of colonial growth patterns is still one of the ways microorganisms are often identified.



http://phil.cdc.gov/phil/details.asp?pid=4428



Scanning electron micrograph of *Mycobacterium tuberculosis*

Key facts

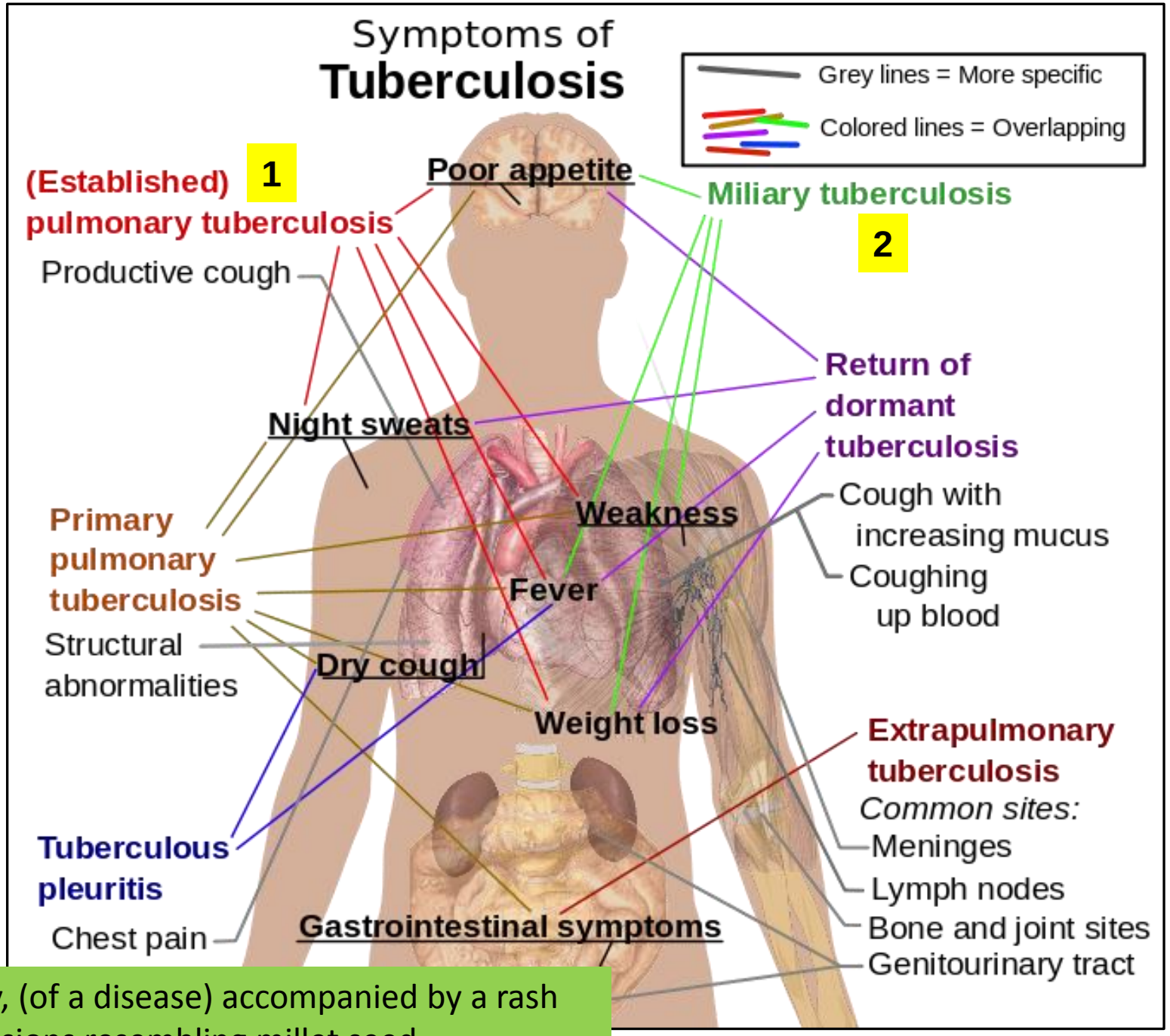
- Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent.

- In 2012, 8.6 million people fell ill with TB and 1.3 million died from TB. Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top three causes of death for women aged 15 to 44. In 2012, an estimated 530 000 children became ill with TB and 74 000 HIV-negative children died of TB.

- TB is a leading killer of people living with HIV causing one quarter of all deaths.

- Multi-drug resistant TB (MDR-TB) is present in virtually all countries surveyed.

- The estimated number of people falling ill with tuberculosis each year is declining, although very slowly, which means that the world is on track to achieve the Millennium Development Goal to reverse the spread of TB by 2015. The TB death rate dropped 45% between 1990 and 2012. An estimated 22 million lives saved through use of DOTS and the Stop TB Strategy recommended by WHO. http://www.who.int/mediacentre/factsheets/fs104/en/index.html



Miliary, (of a disease) accompanied by a rash with lesions resembling millet seed

www.wikipdia.org

Neisseria meningitidis

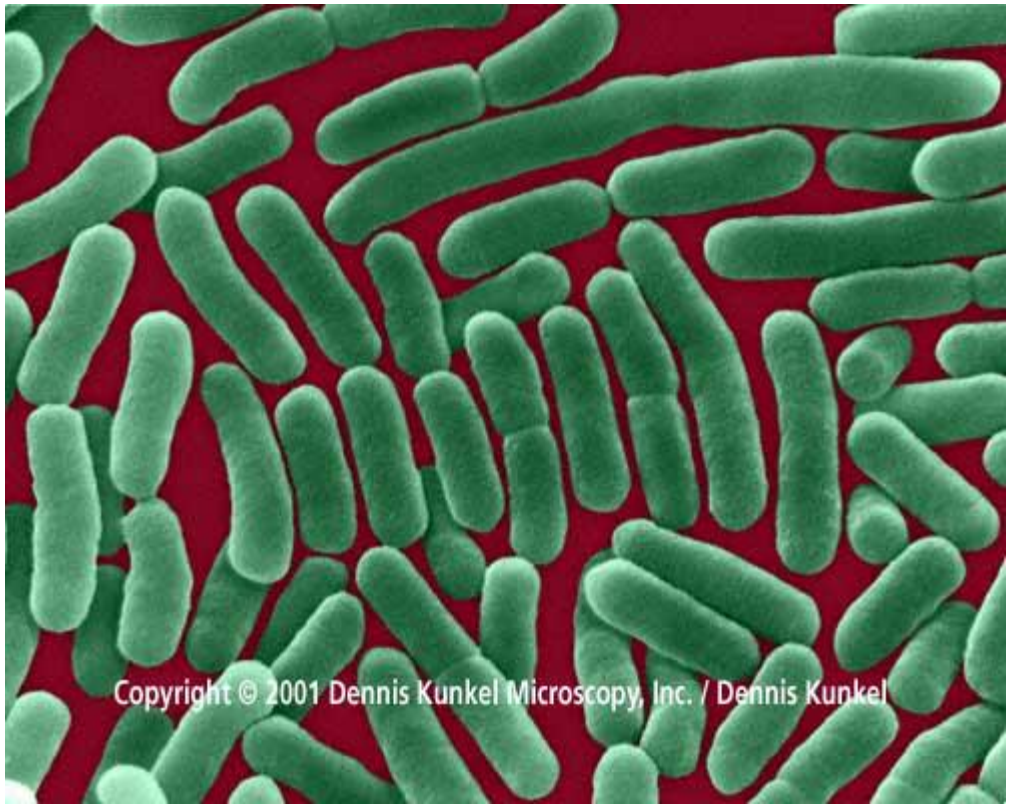
- ***Neisseria meningitidis***, often referred to as ***meningococcus***, is a bacterium that can cause meningitis and other forms of meningococcal disease such as meningococcemia, a life-threatening sepsis.

- *N. meningitidis* is a major cause of morbidity and mortality during childhood in industrialized countries and has been responsible for epidemics in Africa and in Asia.

- Upon Gram staining, it appears as a Gram-negative diplococcus and cultures of the bacteria test positive for the enzyme cytochrome c oxidase. It exists as normal flora (nonpathogenic) in the nasopharynx of up to 5–15% of adults. It causes the only form of bacterial meningitis known to occur epidemically.

- *Streptococcus pneumoniae* (aka *pneumococcus*) is the most common bacterial etiology of meningitis in children beyond 2 months of age (1–3 per 100,000). Meningococci only infect humans and have never been isolated from animals because the bacterium cannot get iron other than from human sources (transferrin and lactoferrin)

Salmonella enterica
subsp. *enterica*



Salmonella enterica* subsp. *enterica is a subspecies of *Salmonella enterica*, the rod-shaped, flagellated, aerobic, Gram-negative bacterium.

It is a member of the genus *Salmonella*.

Many of the pathogenic serovars of the *S. enterica* species are in this subspecies.

- **Typhoid fever** — also known simply as typhoid — is a common worldwide bacterial disease transmitted by the ingestion of food or water contaminated with the feces of an infected person, which contain the bacterium *Salmonella enterica enterica*, serovar Typhi.

- The disease has received various names, such as gastric fever, abdominal typhus, infantile remittant fever, slow fever, nervous fever and pythogenic fever.

- The name *typhoid* means "resembling typhus" and comes from the neuropsychiatric symptoms common to typhoid and typhus. Despite this similarity of their names, typhoid fever and typhus are distinct diseases and are caused by different species of bacteria.

- The impact of this disease fell sharply in the developed world with the application of 20th-century sanitation techniques.

- **Typhoid vaccines** are vaccines developed to prevent typhoid fever.

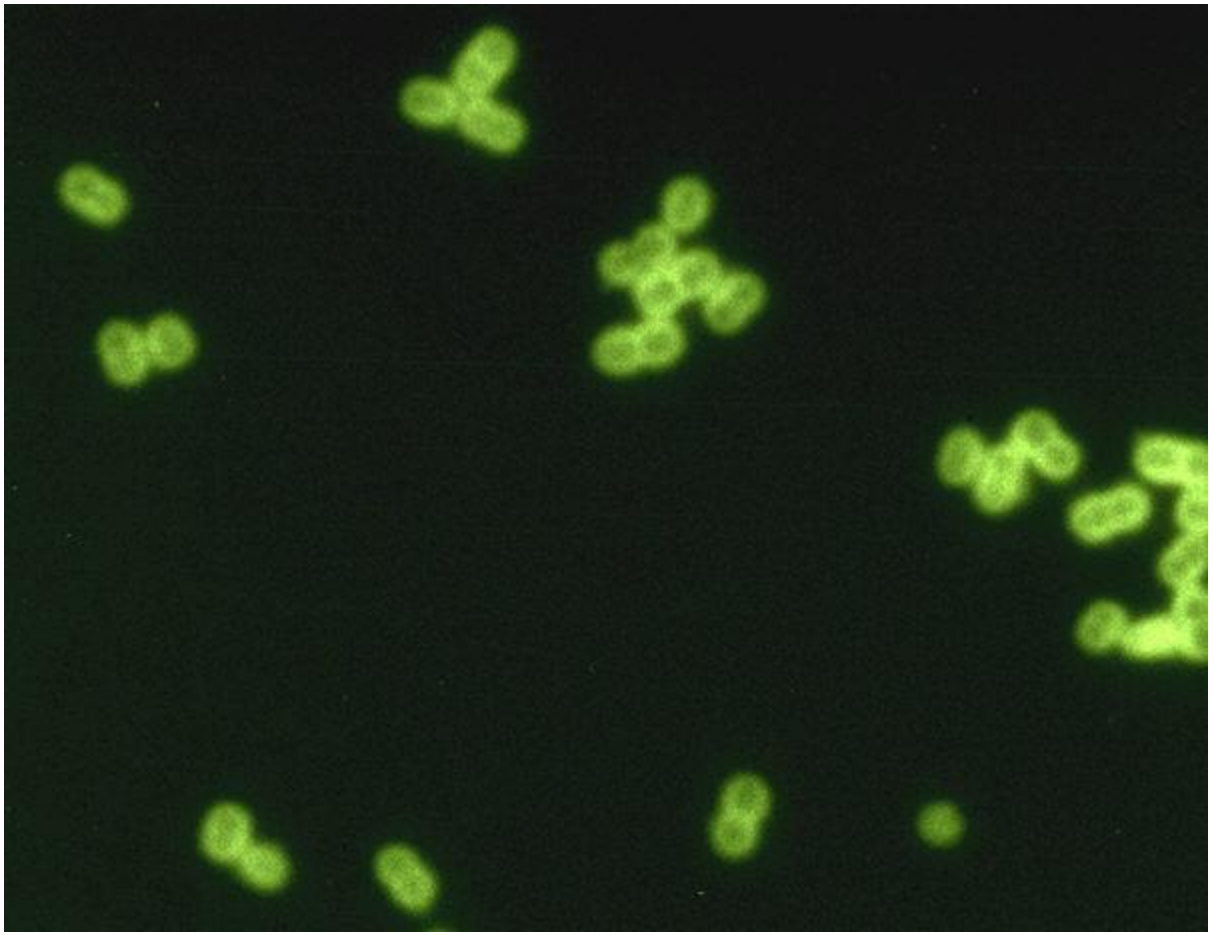
- There are two effective types:

Ty21a, which is a live vaccine given orally and Vi capsular polysaccharide vaccine, which is an injectable subunit vaccine. Ty21a is licensed for use from age six years and older. Boosters are recommended every 5 years. The Vi capsular polysaccharide vaccine is licensed for use from age two years and older, and boosters are required every three years.

- **Available preparations** Vi polysaccharide vaccine:
  Typhim Vi® (Sanofi Pasteur)
  Typherix® (GSK).

- Combined hepatitis A/Vi polysaccharide vaccine:
  ViATIM® (Sanofi Pasteur)
  Hepatyrix® (GSK) Ty21a oral vaccine
  Vivotif® (Crucell)

Streptococcus pneumoniae
Pneumococcus



Streptococcus pneumoniae in spinal fluid. Fluorescent antibody stain.

http://phil.cdc.gov/phil/details.asp?pid=1003

- ***Streptococcus pneumoniae***, or **pneumococcus**, is a Gram-positive, alpha-hemolytic, aerotolerant, anaerobic member of the genus *Streptococcus*.

- A significant human pathogenic bacterium, *S. pneumoniae* was recognized as a major cause of pneumonia in the late 19th century, and is the subject of many humoral immunity studies.

- *S. pneumoniae* resides asymptomatically in the nasopharynx of healthy carriers. However, in susceptible individuals, such as elderly and immunocompromised people and children, the pathogen can spread to other locations and cause disease. *S. pneumoniae* is the main cause of community acquired pneumonia and meningitis in children and the elderly, and of septicemia in HIV-infected persons.

- Despite the name, the organism causes many types of pneumococcal infections other than pneumonia. These invasive pneumococcal diseases include acute sinusitis, otitis media, conjunctivitis, meningitis, bacteremia, sepsis, osteomyelitis, septic arthritis, endocarditis, peritonitis, pericarditis, cellulitis, and brain abscess.

- **Pneumococcal conjugate vaccine** (**PCV**) is a pneumococcal vaccine used to protect infants and young children against disease caused by the bacteria *Streptococcus pneumoniae* (pneumococcus).

- There are currently three PCV vaccines available on the global market: **Prevnar** (called Prevenar in some countries), **Synflorix** and **Prevnar 13**. **Prevnar** is a *hepta*valent vaccine, meaning that it contains the cell membrane sugars of seven serotypes of pneumococcus, conjugated with Diphtheria proteins. It was manufactured by Wyeth.

- In the United States, vaccination with Prevnar is recommended for all children younger than 2 years, and for unvaccinated children between 24 and 59 months old who are at high risk for pneumococcal infections.

Vibrio cholerae

Key facts

- **Cholera** is an acute diarrhoeal disease that can kill within hours if left untreated.

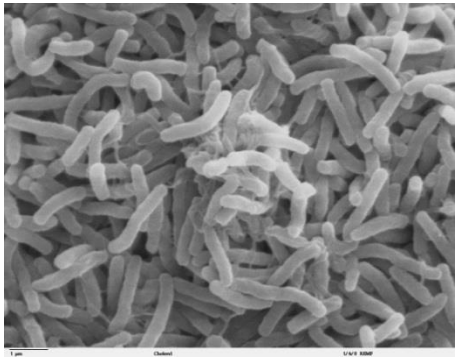
- There are an estimated 3–5 million cholera cases and 100 000–120 000 deaths due to cholera every year.

- Up to 80% of cases can be successfully treated with oral rehydration salts. Effective control measures rely on prevention, preparedness and response.

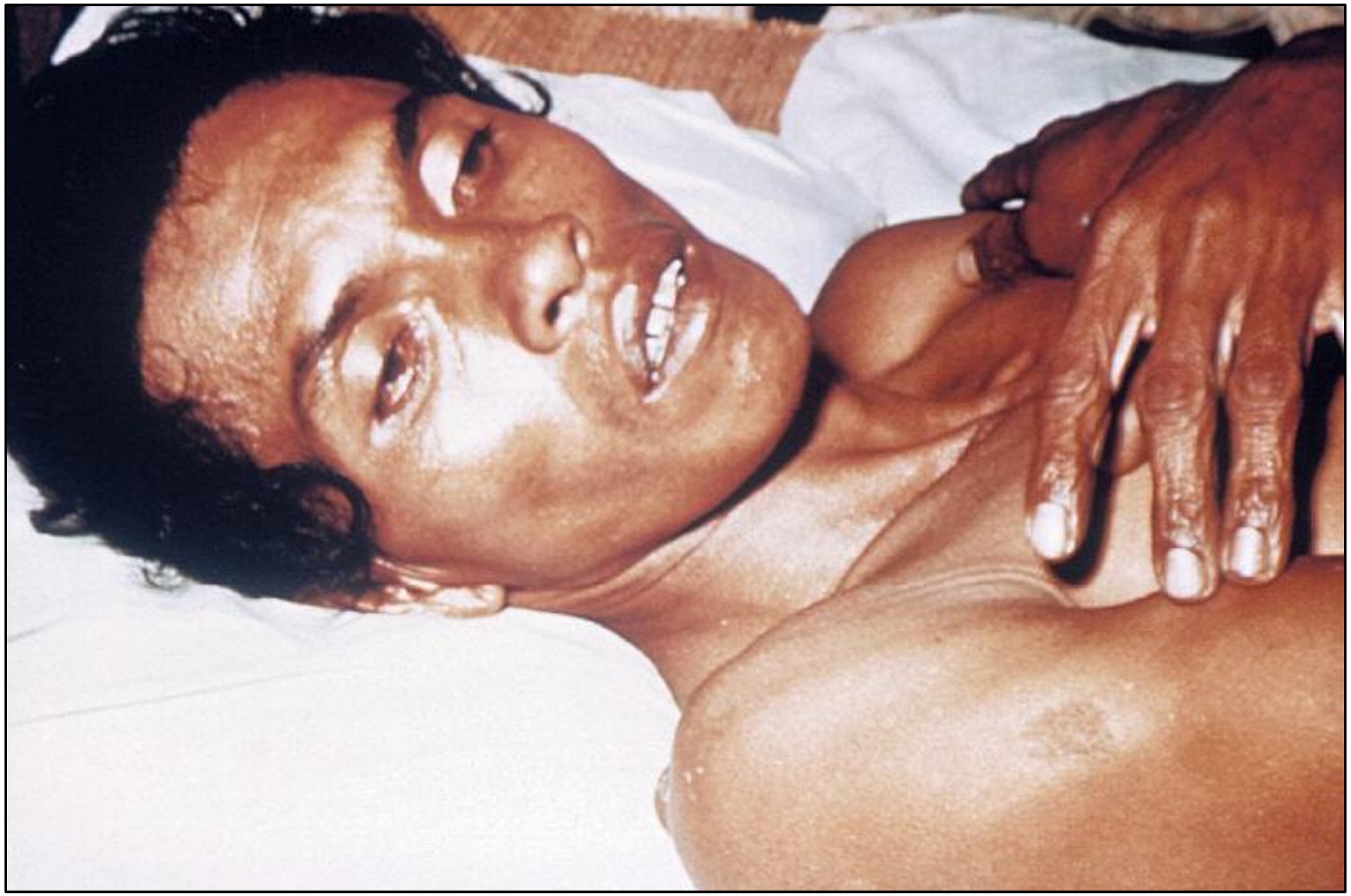
- Provision of safe water and sanitation is critical in reducing the impact of cholera and other waterborne diseases.

- Oral cholera vaccines are considered an additional means to control cholera, but should not replace conventional control measures.

World Health Organization



A patient with cholera



A person with severe dehydration due to cholera. Note the sunken eyes and decreased skin turgor which produces wrinkled hands and skin.

Cholera vaccine

- The first vaccines used against cholera were developed in the late nineteenth century.

- These injected whole cell vaccines became increasingly popular until they were replaced by oral vaccines starting in the 1980s.

- Both oral and injectable forms are about 50-60% effective in the first year.

Parasitic diseases and vaccines

Malaria

- **Malaria** is a potentially deadly disease caused by infection with the microscopic parasite ***Plasmodium***.

- *Plasmodium* is transmitted to humans through bites from *Anopheles* mosquitoes infected with the parasite.

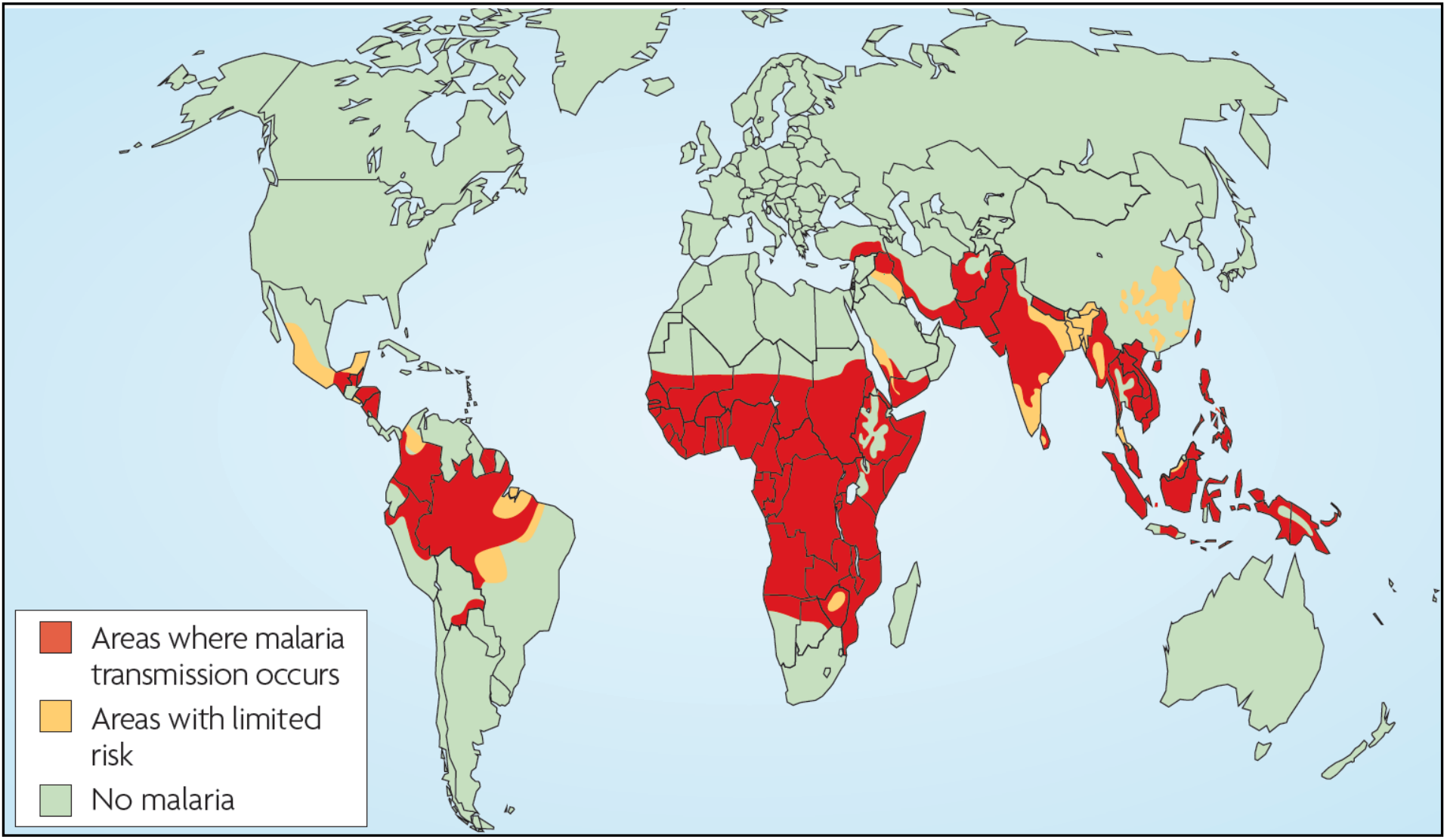
- According to the World Health Organization, malaria is present in more than 100 countries—mostly in sub-Saharan Africa and Southeast Asia.

- Each year there are roughly 300 million cases of malaria, and more than 1 million people die of the disease.

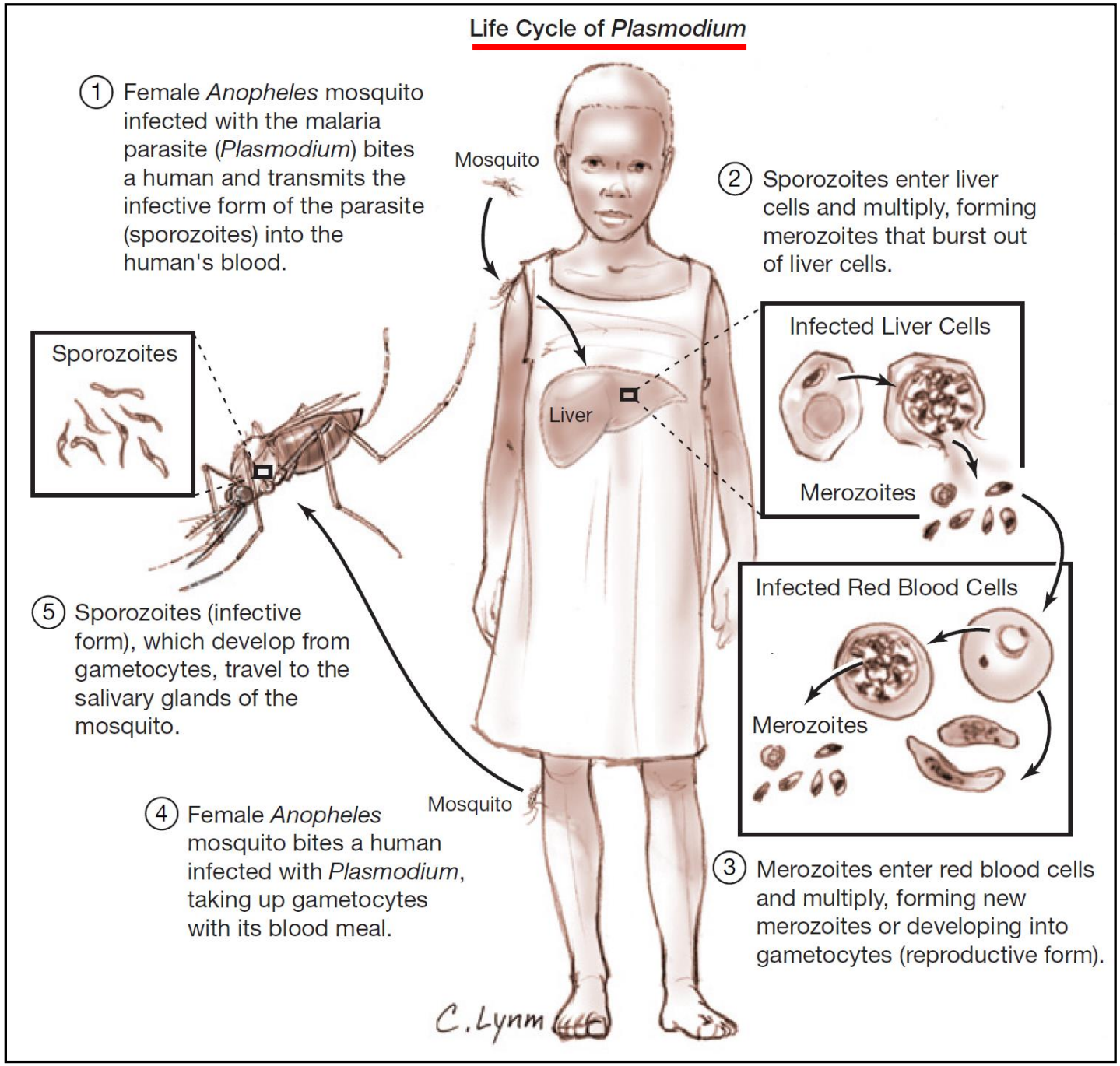
- Children and pregnant women are especially at risk for malaria.

Parmet S et al, JAMA, PATIENT PAGE, 2005

Global distribution of malaria incidence



Todryk & Hill, Nature Rev Microbiol, 2007



Parmet S et al, JAMA, PATIENT PAGE, 2005

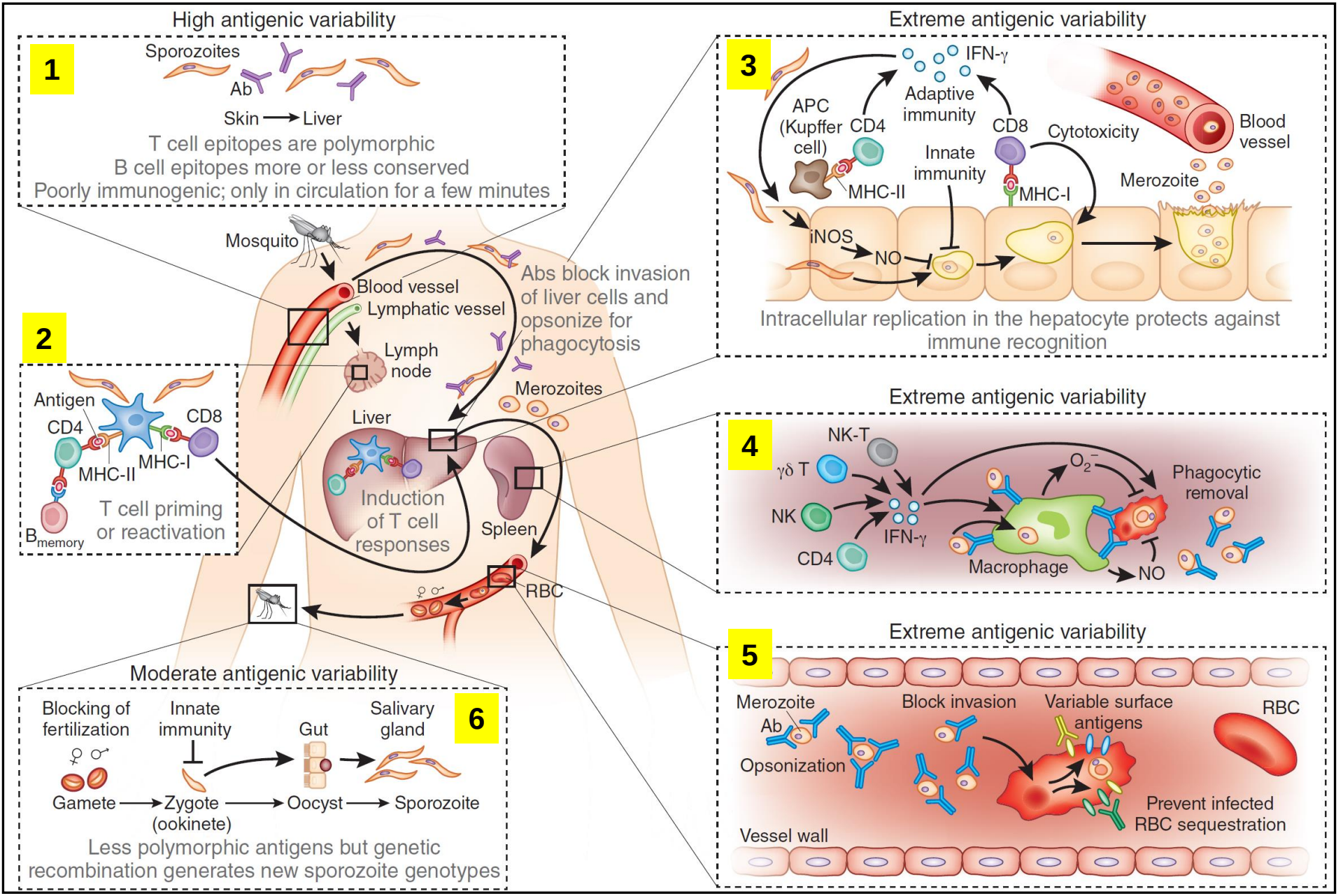
SYMPTOMS

Symptoms usually appear about 9 to 14 days after being bitten by an infected mosquito.

- Sudden, violent chills
- Intermittent fever
- Sweating
- Exhaustion
- Headaches
- Seizures
- Delirium

Parmet S et al, JAMA, PATIENT PAGE, 2005

Life cycle of *Plasmodium* spp. infections, with the main immune responses that control the parasite at each stage



Riley & Stewart, Nature Med, 2013

Malaria vaccine approaches: aims and required immune responses

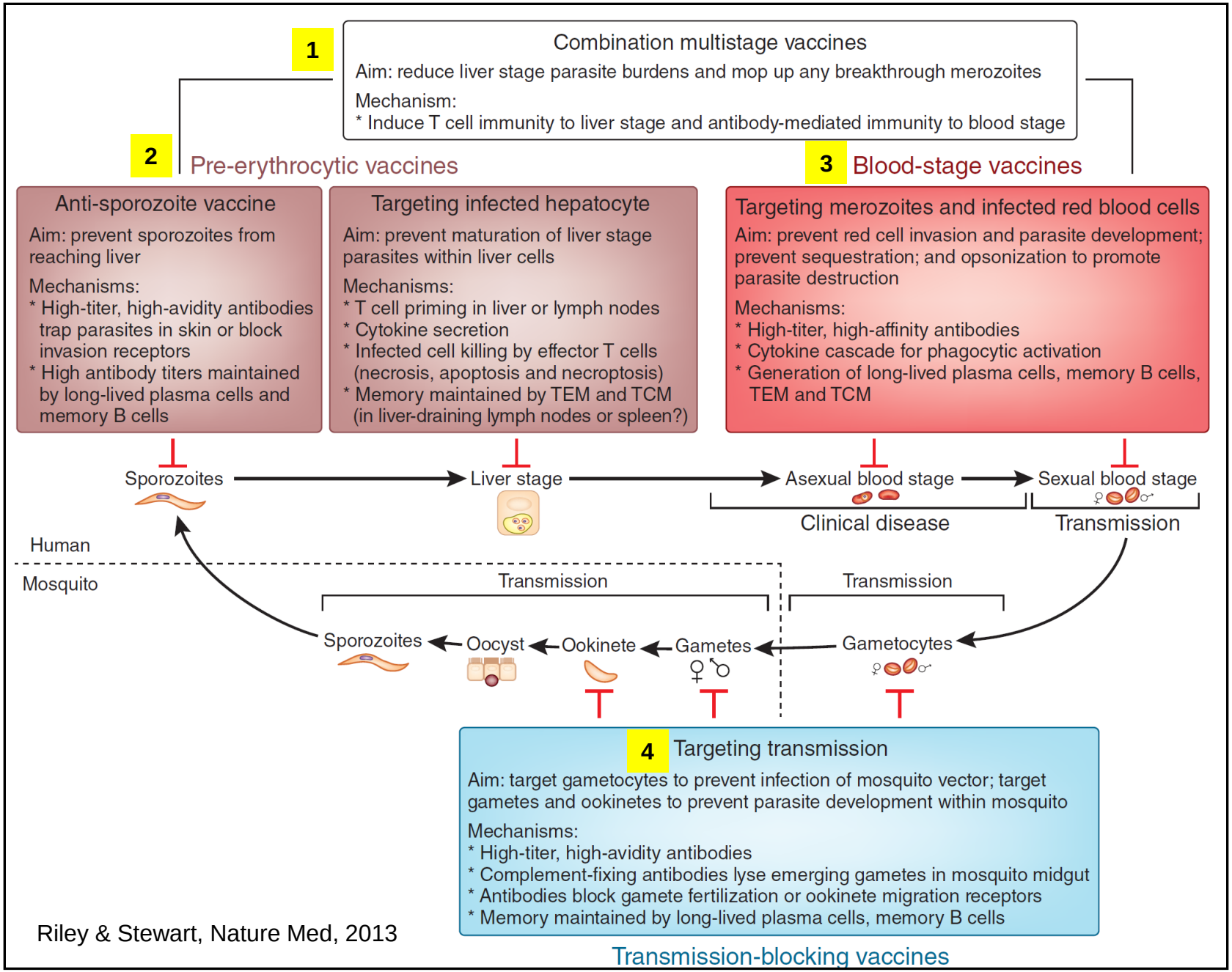


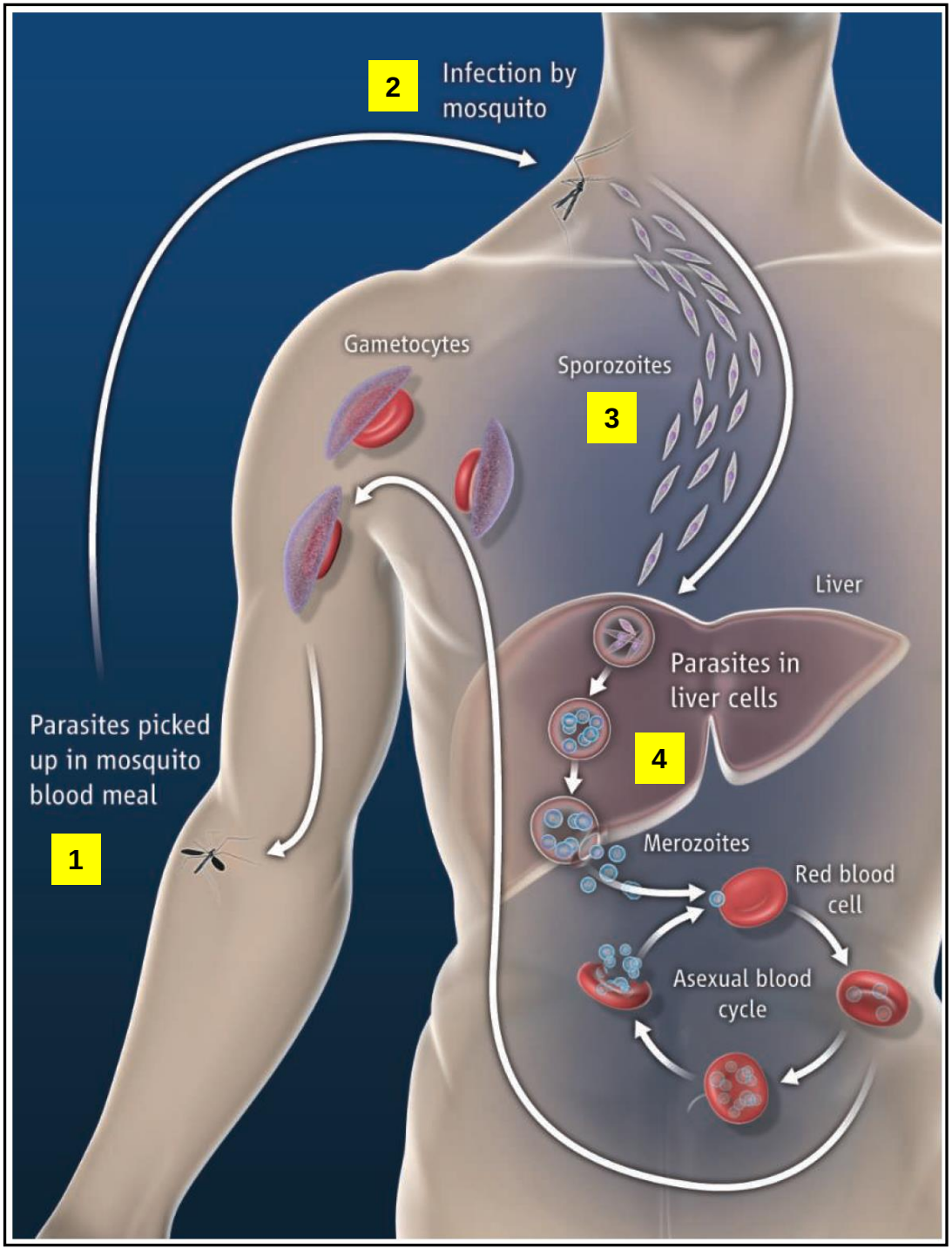
Figure 3 TEM, effector memory T cells; TCM, central memory T cells

IMMUNOLOGY

Pasteur Approach to a Malaria Vaccine May Take the Lead

Michael F. Good

A rationalized and reinvented approach to vaccinating against malaria shows impressive results.

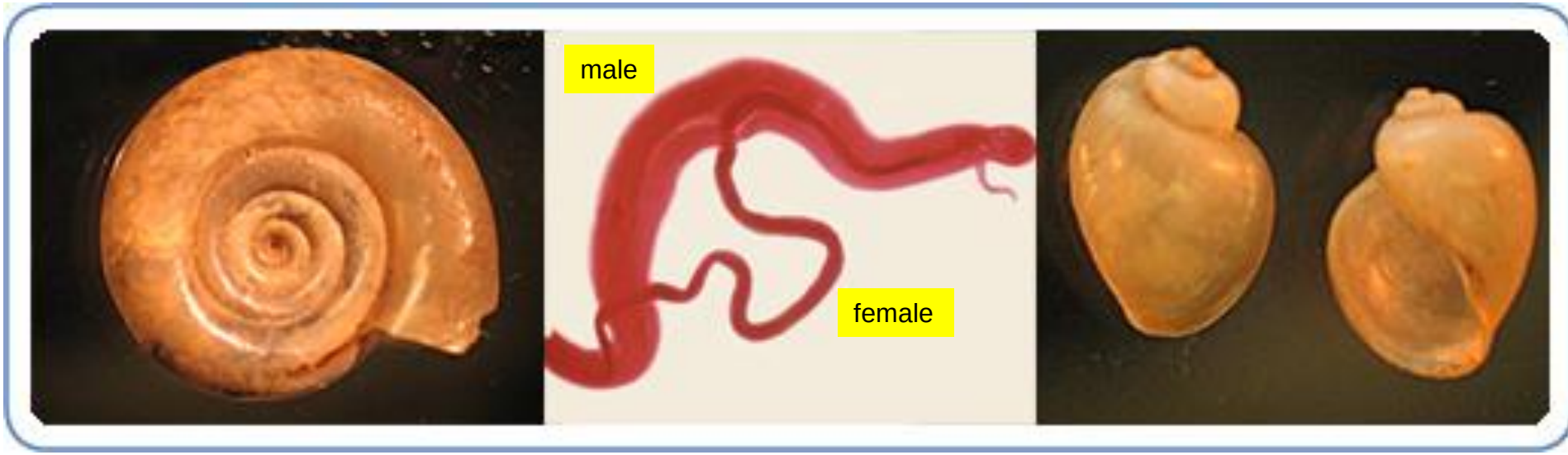


Malaria life cycle

A high dose of irradiated sporozoites delivered intravenously shows promising results as a vaccine.

Good MF, Science, 2013

Schistosomiasis



- Schistosomiasis, also known as bilharzia, is a disease caused by parasitic worms. Although the worms that cause schistosomiasis are not found in the United States, more than 200 million people are infected worldwide. In terms of impact this disease is second only to malaria as the most devastating parasitic disease. Schistosomiasis is considered one of the Neglected Tropical Diseases.

- The parasites that cause schistosomiasis live in certain types of freshwater snails. The infectious form of the parasite, known as cercariae, emerge from the snail, hence contaminating water. You can become infected when your skin comes in contact with contaminated freshwater. Most human infections are caused by *Schistosoma mansoni, S. haematobium*, or *S. japonicum*.

Image: ***Left:*** Biomphalaria *sp., the intermediate host for* S. mansoni*.* ***Right:*** Bulinus *sp., the intermediate host for* S. haematobium *and* S. intercalatum*.* ***Center:*** *Adults of* S. mansoni*. The thin female resides in the gynecophoral canal of the thicker male. Credit: DPDx*

http://www.cdc.gov/parasites/schistosomiasis/

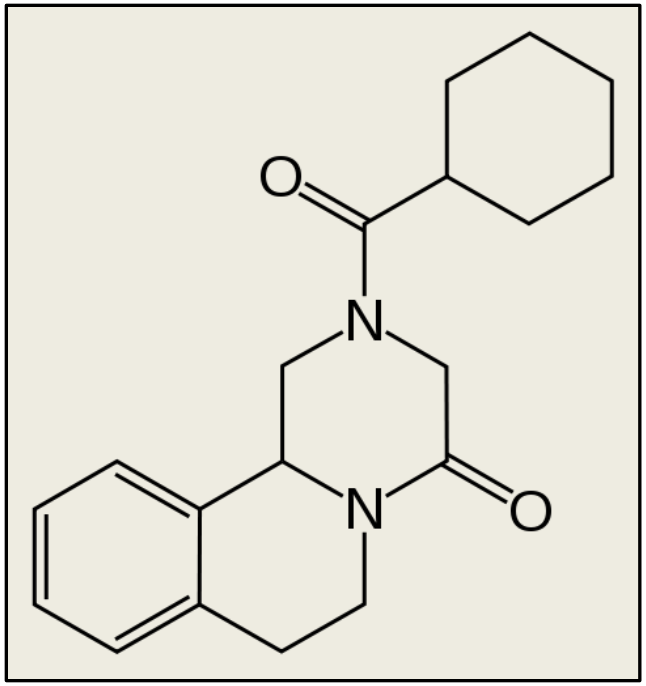
Key facts

- Schistosomiasis is a chronic disease caused by parasitic worms.
- At least 243 million people required treatment for schistosomiasis in 2011.
- People are at risk of infection due to agricultural, domestic and recreational activities which expose them to infested water.
- Lack of hygiene and play habits make children especially vulnerable to infection.
- Clean drinking water, adequate sanitation and hygiene education would reduce infective water contact and the contamination of water sources.

http://www.who.int/mediacentre/factsheets/fs115/en/index.html

Key facts (cont.)

- Schistosomiasis control focuses on reducing disease through periodic, large-scale population treatment with praziquantel.



Praziquantel (**Biltricide**), an antihelmintic effective against flatworms.

http://www.who.int/mediacentre/factsheets/fs115/en/index.html

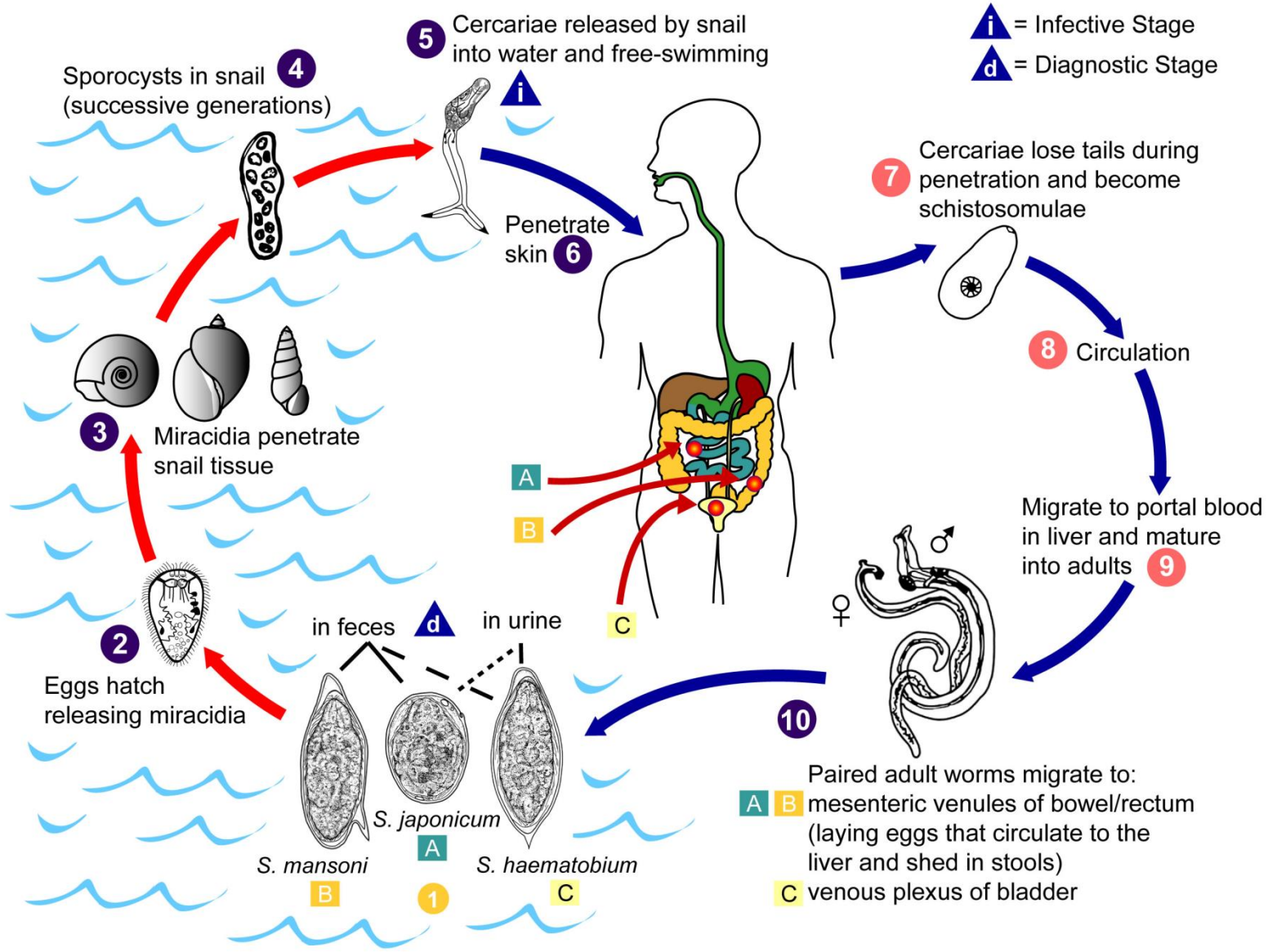
Transmission of schistosomiasis

- People become infected when larval forms of the parasite – released by freshwater snails – penetrate the skin during contact with infested water.

- In the body, the larvae develop into adult schistosomes. Adult worms live in the blood vessels where the females release eggs. Some of the eggs are passed out of the body in the faeces or urine to continue the parasite life-cycle. Others become trapped in body tissues, causing an immune reaction and progressive damage to organs.

http://www.who.int/mediacentre/factsheets/fs115/en/index.html

Schistosomiasis



www.wikipedia.org

Parasite species and geographical distribution of schistosomiasis

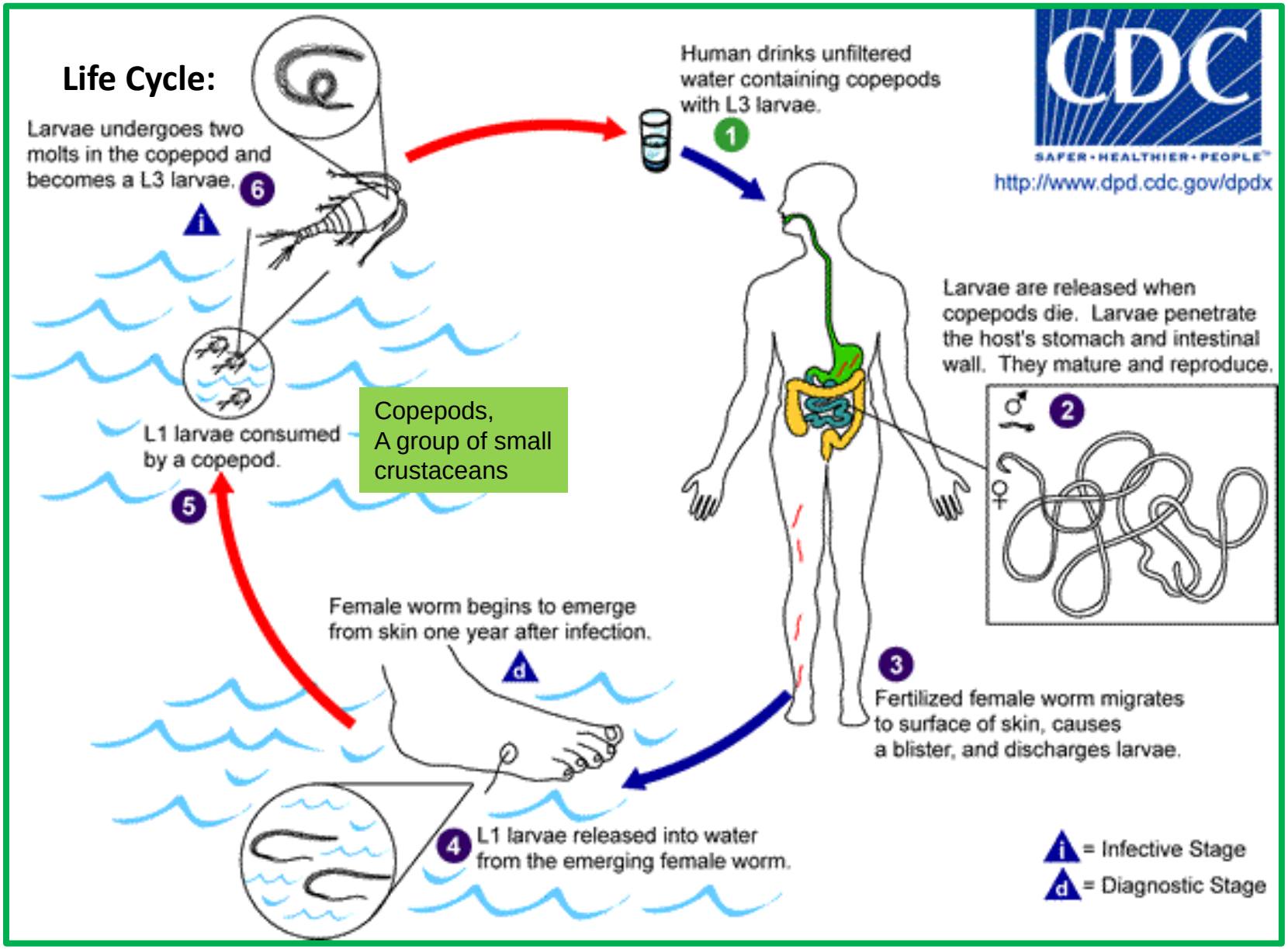
	Species	Geographical distribution
Intestinal schistosomiasis	*Schistosoma mansoni*	Africa, the Middle East, the Caribbean, Brazil, Venezuela, Suriname
	Schistosoma japonicum	China, Indonesia, the Philippines
	Schistosoma mekongi	Several districts of Cambodia and the Lao People's Democratic Republic
	Schistosoma guineensis and related *S. intercalatum*	Rain forest areas of central Africa
Urogenital schistosomiasis	*Schistosoma haematobium*	Africa, the Middle East

http://www.who.int/mediacentre/factsheets/fs115/en/index.html

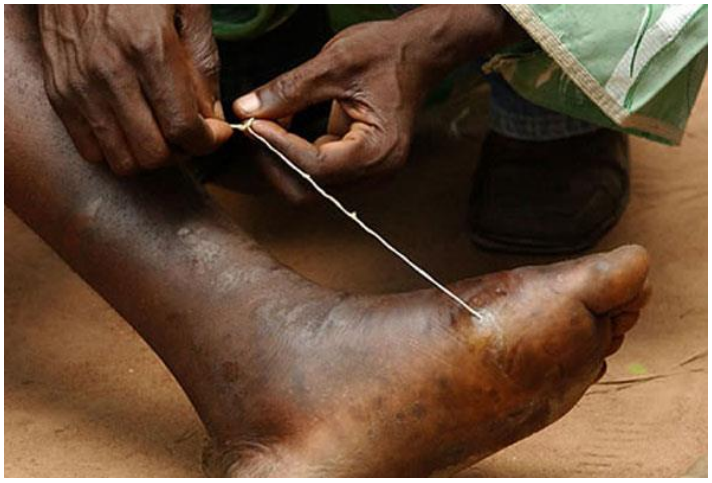
Guinea worm disease

Causal Agent:

Dracunculiasis (guinea worm disease) is caused by the nematode (roundworm) *Dracunculus medinensis*.



Guinea Worm Eradication Program



http://www.monitor.co.ug/Magazines/Health---Living/-/689846/833242/-/qvbby6/-/index.html

Clean, safe drinking water is of key importance in prevention and eradication Guinea worm disease.

http://www.cartercenter.org/index.html

THE CARTER CENTER

Waging Peace. Fighting Disease. Building Hope.

PEACE PROGRAMS HEALTH PROGRAMS COUNTRIES ABOUT US NEWS & PUBLICATIONS GET INVOLVED WAYS TO GIVE

http://www.cartercenter.org/index.html

Results and Impact

- Incidences of Guinea worm disease have been reduced from an estimated 3.5 million in 1986 to 148 in 2013.

- The Guinea worm eradication campaign has averted at least 80 million cases of this devastating disease among the world's poorest and most neglected people.

- The campaign has helped to establish village-based health delivery systems in thousands of communities that now have networks of health personnel and volunteers to provide health education and interventions to prevent other diseases as well.

Immune Evasion by Parasites

Parasites evade protective immunity by reducing their immunogenicity and by inhibiting host immune responses.

- Different parasites have developed remarkably effective ways of resisting immunity.

- Parasites become resistant to immune effector mechanisms during their residence in vertebrate hosts. Perhaps the best examples are schistosome larvae, which travel to the lungs of infected animals and during this migration develop a tegument that is resistant to damage by complement and by CTLs. The biochemical basis of this change is not known.

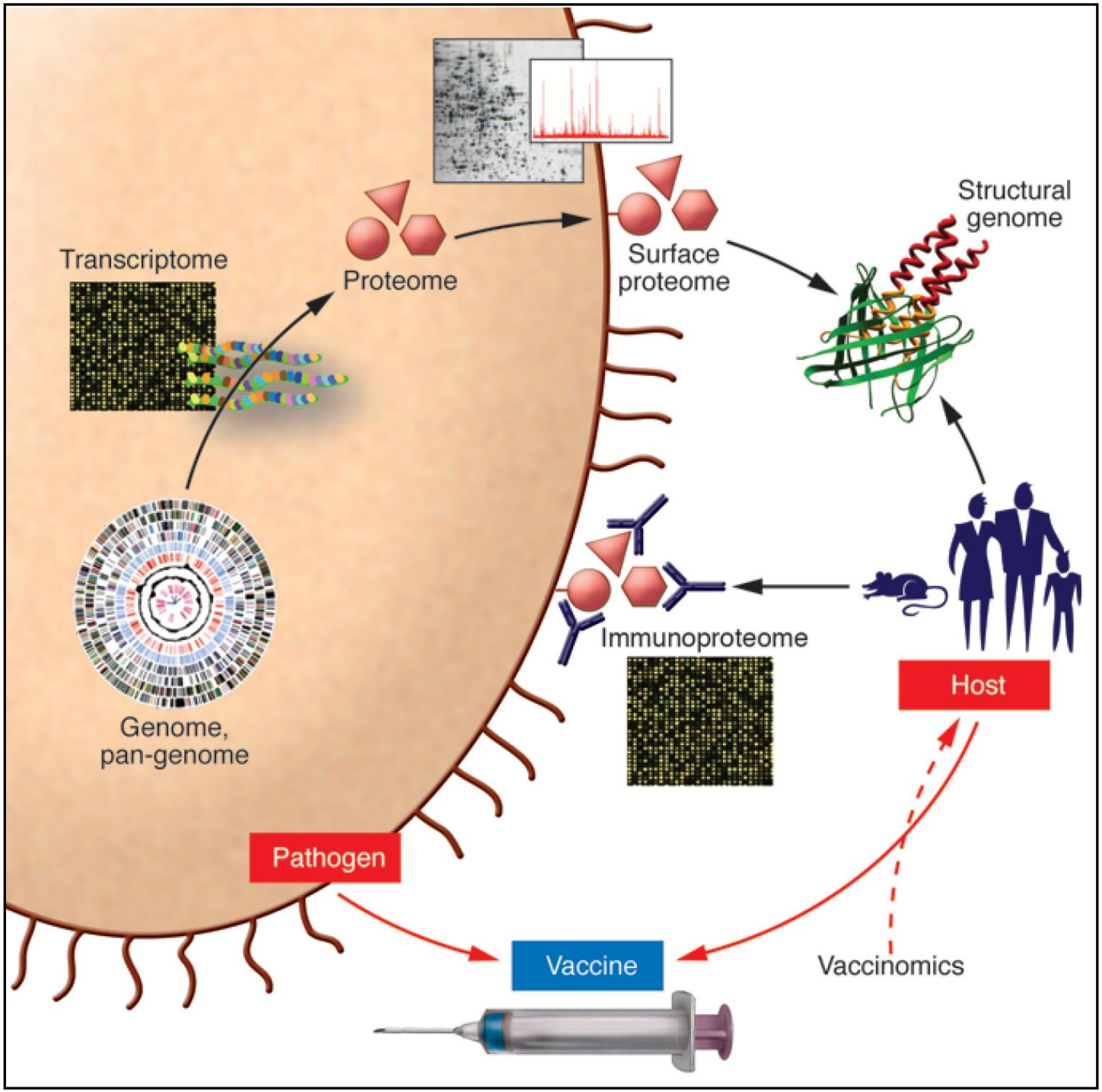
TABLE 15–5 Mechanisms of Immune Evasion by Parasites

Mechanism of Immune Evasion	Examples
Antigenic variation	Trypanosomes, *Plasmodium*
Acquired resistance to complement, CTLs	Schistosomes
Inhibition of host immune responses	Filaria (secondary to lymphatic obstruction), trypanosomes
Antigen shedding	Entamoeba

CTL, cytotoxic T lymphocyte.

Abbas, Lichtman, Pillai: Cellular and Molecular Immunology, 7th Edition, 2012.

Identification of vaccine candidates in the genome era



Schematic overview of the way in which high-throughput analyses applied to various aspects of a pathogen and its interactions with the host immune system are used to identify vaccine candidates in the genome era.

Rinaudo CD et al,

J Clin Invest, 2009

Vaccines under research (1)

Adenovirus
Alzheimer's disease amyloid protein
Aeromonas hydrophila
Bartonellosis
Borrelia miyamotoi
Burkholderia mallei
Cancer
Caries
Chagas disease
CD47-blocking antibodies anti-cancer vaccine
Chlamydia
Coxsackie A virus
Coxsackie B virus
Chlamydophila pneumoniae
Cryptococcus neoformans
Coccidioidomycosis
Coxsackie A virus
Coxsackie B virus
Campylobacter
Cytomegalovirus
Ebola virus disease
Echovirus
Enterobacter
Enterovirus 71
Epstein–Barr vaccine
Ehrlichiosis
Fasciolopsiasis

Wikipedia

Vaccines under research (2)

- Hepatitis C
- HIV
- H7N9
- Hookworm vaccine
- Human adenovirus type-3
- Haemophilus ducreyi
- Jamestown Canyon virus (JCV) and Powassan virrus.
- Klebsiella pneumoniae
- Leprosy
- Lyme disease
- Listeria monocytogenes
- Leishmania
- Malaria
- Molluscum contagiosum
- Marburg virus disease
- Human metapneumovirus (hMPV)
- Middle East Respiratory Syndrome (MERS)
- murine leukemia virus (MLV) vaccine research and anti-cancer research
- Norovirus
- Schistosomiasis vaccine
- Staphylococcus aureus
- Toxoplasma gondii vaccine research for cats and humans
- Tularemia vaccine
- Trypanosomiasis
- Treponema pallidum
- Trichinella britovi

H7N9, Influenza A virus subtype H7N9

Wikipedia

Vaccines under research (3)

- Trichinella nativa
- T. nelsoni
- Trichomonas vaginalis
- Trichuris trichiura
- Trichinella spiralis
- Visceral leishmaniasis
- Dengue fever
- Eastern Equine encephalitis virus
- HTLV-1
- HTLV-2
- Onchocerciasis
- Respiratory syncytial virus
- Rotavirus
- Severe acute respiratory syndrome (SARS)
- Scarlet fever
- Streptococcus pyogenes
- SV40 Simian vacuolating virus 40
- Syphilis
- Sindbis
- TMAdV
- Tularemia
- Trichomoniasis
- Venezuelan equine encephalitis virus
- Visceral leishmaniasis
- West Nile virus vaccine
- Yersinia pestis

Zika virus

HTLV, Human T-cell lymphotropic virus
SV40, Simian virus 40
TMAdV, Titi monkey adenovirus
T. nelsoni, Trichinella nelsoni

Wikipedia