INFECTIOUS DISEASE:
OVERVIEW AND UPDATE

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OBJECTIVES

- Understand the difference between bacteria, viruses, and fungi, and parasites
- Understand how the immune system responds to pathogens
- Review different types of vaccines
- Understand which pathogens are most concerning for corneal transplant
- Apply understanding of infectious diseases to the review of medical charts

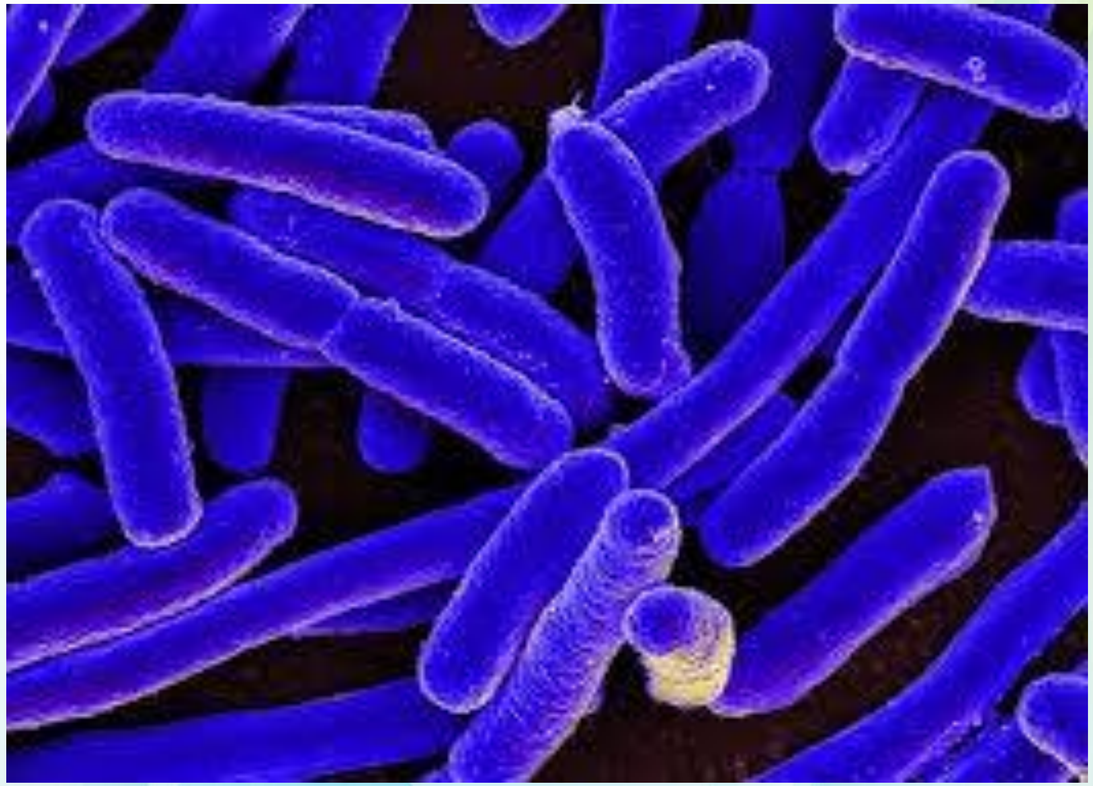
INFECTIONS

Bacteria, fungus, virus, parasite…what's the difference and should I care?

Bacteria

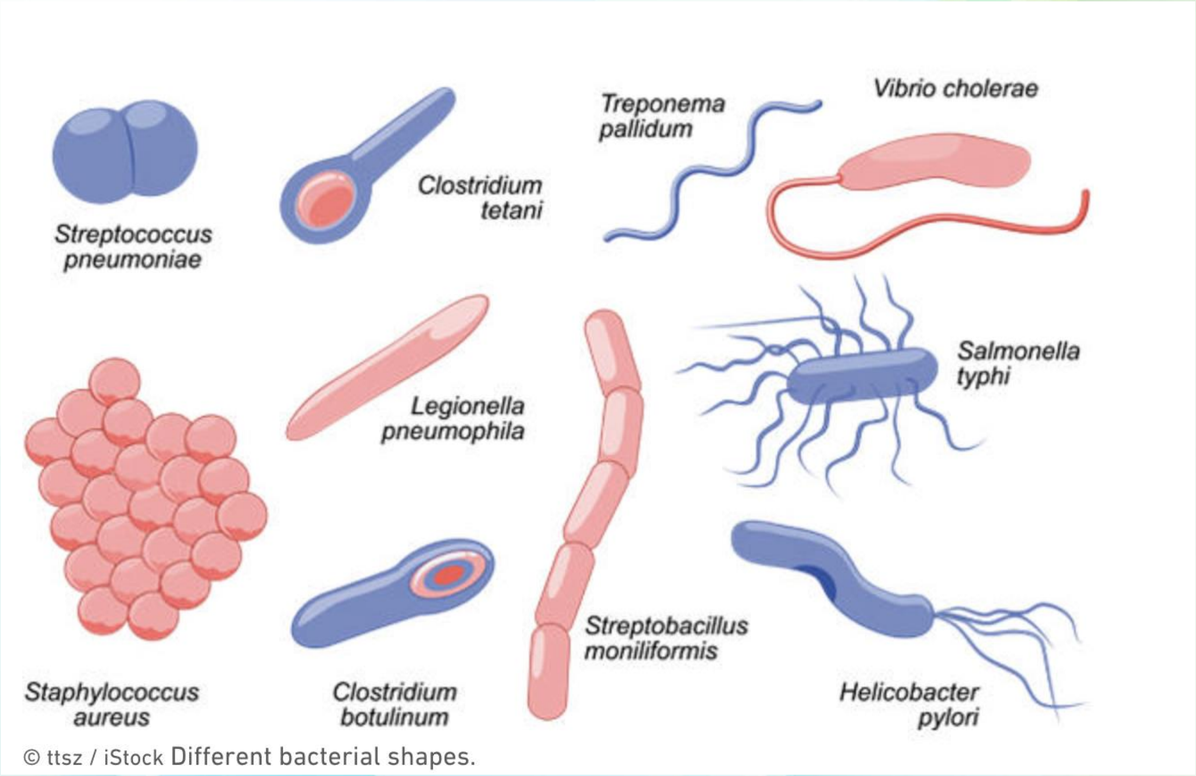
- Large group of single-celled organisms
- Ubiquitous
- Vital to ecosystem
- Prokaryote (bacterial DNA floats freely within the cell)
- Structure: 5 basic shapes:

Spherical (cocci)
Rod (bacilli)
Spiral (spirilla)
Comma (vibrios)
Corkscrew (spirochetes)

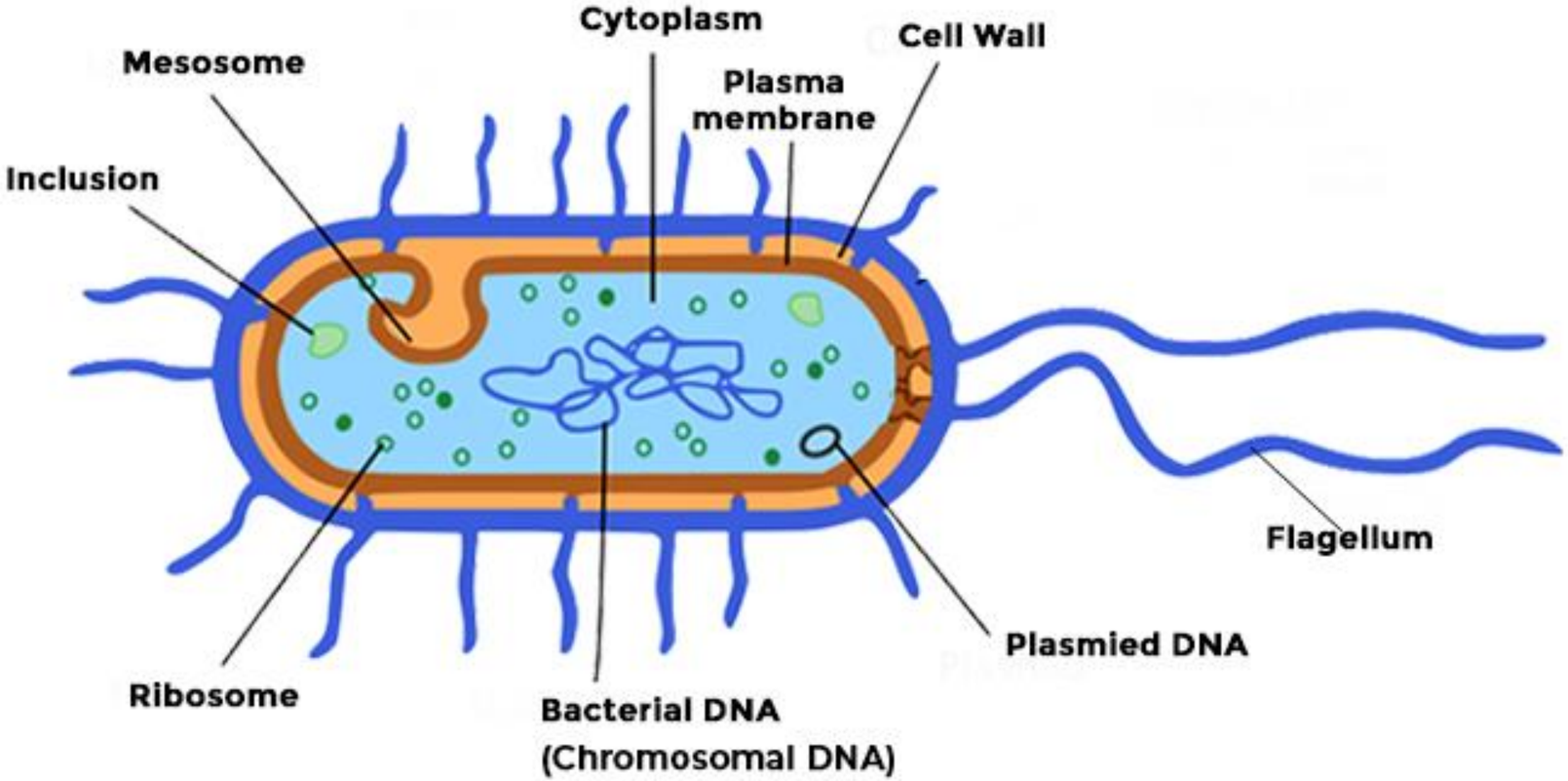


Bacteria

- Humans/other animals carry vast numbers of bacteria, most in gut
- Most are harmless, many beneficial
- Many species are pathogenic or have the potential to be pathogenic



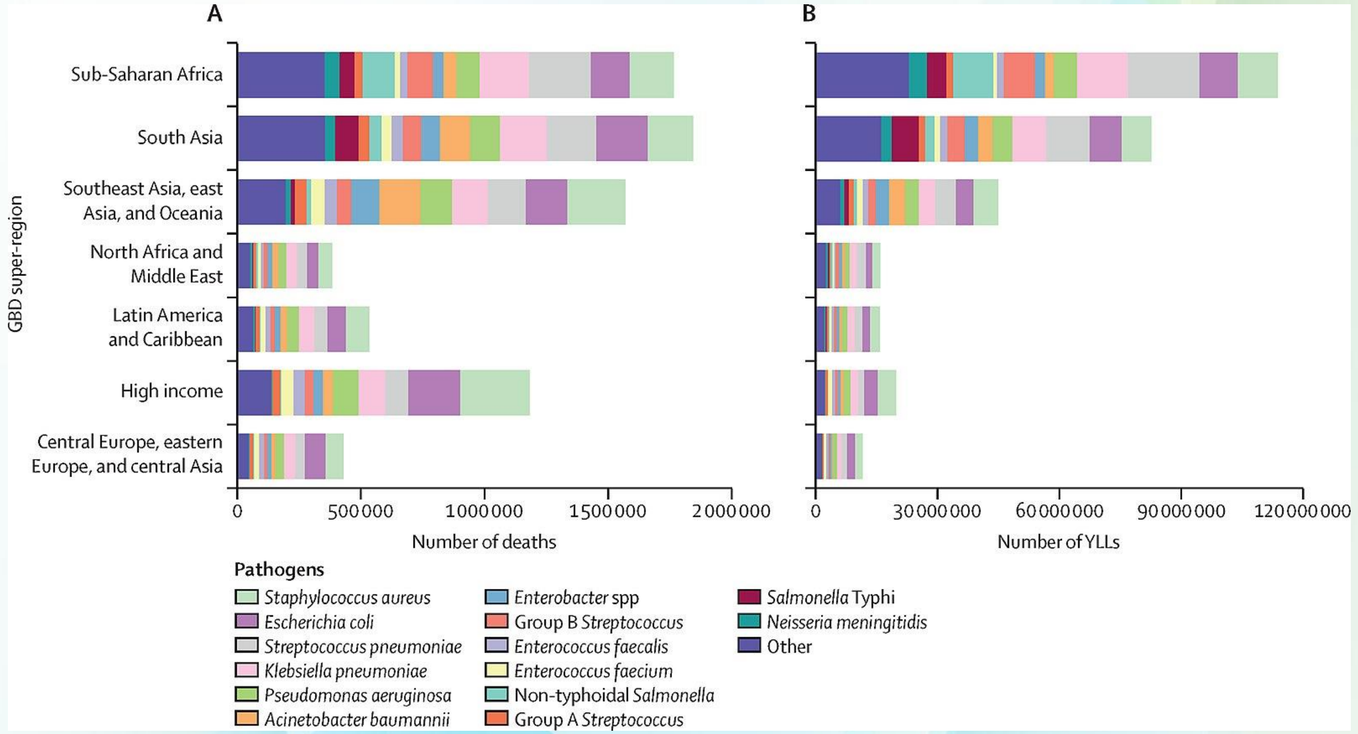
© ttsz / iStock Different bacterial shapes.



https://www.pw.live/biology-articles/bacteria

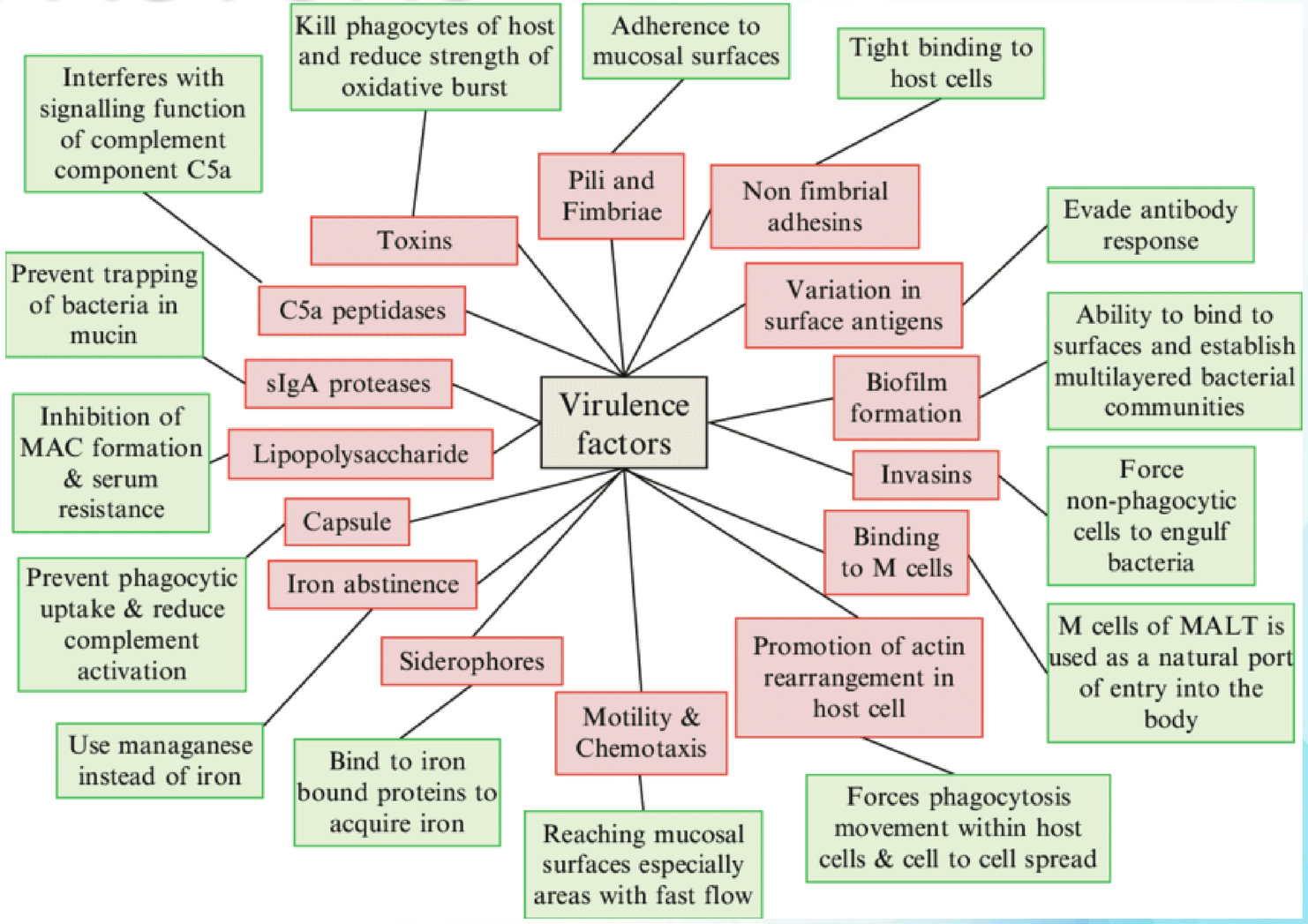
Common Bacterial Pathogens (Worldwide)

- Mycobacterium tuberculosis
- Staphylococcus
- Streptococcus
- Pseudomonas
- Shigella
- Campylobacter
- Typhoid
- Diptheria



By Authors of the study: GBD 2019 Antimicrobial Resistance Collaborators - https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02185-7/fulltext, CC BY 4.0, https://commons.wikimedia.org/w/index.php?curid=127577217

BACTERIAL VIRULENCE FACTORS

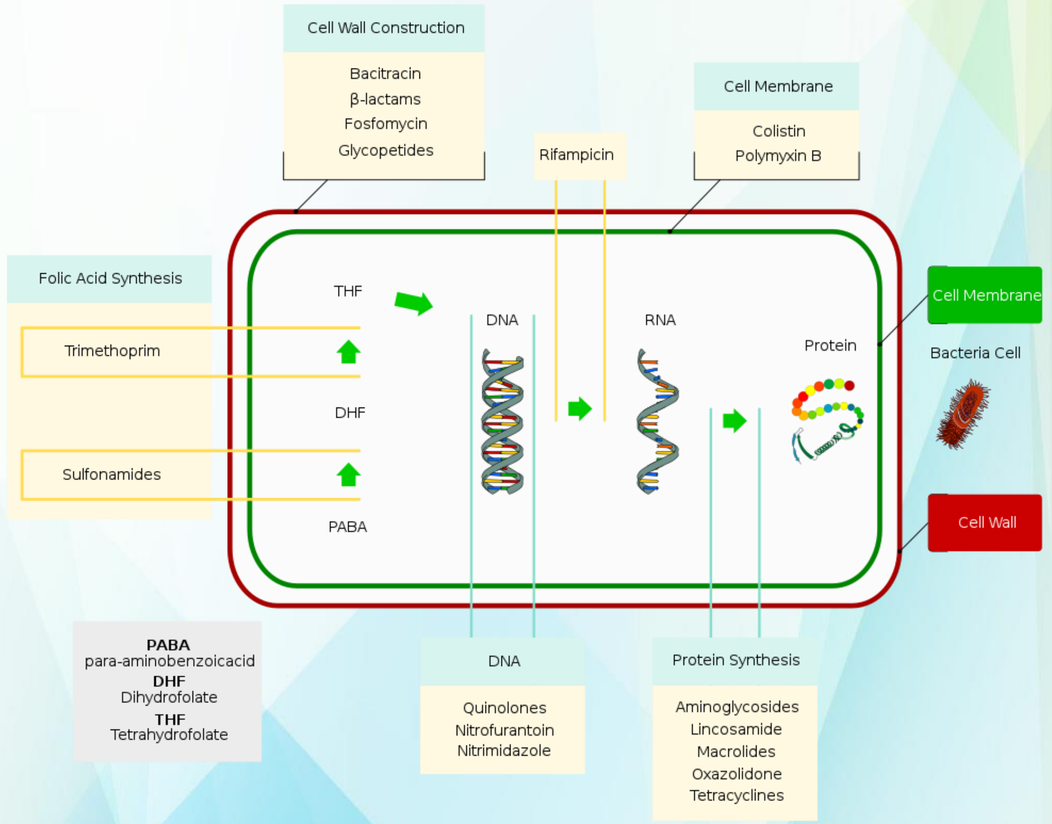


- Toxin production
- Structure of bacteria
- Enzymes

Viswanathan, Pragasam & Suneeva, S.C. & Rathinam, Prasanth. (2015). Quorum Sensing in Pathogenesis and Virulence. Quorum Sensing vs Quorum Quenching: A Battle with no end in Sight. 39-50. 10.1007/978-81-322-1982-8__4.

TREATMENT

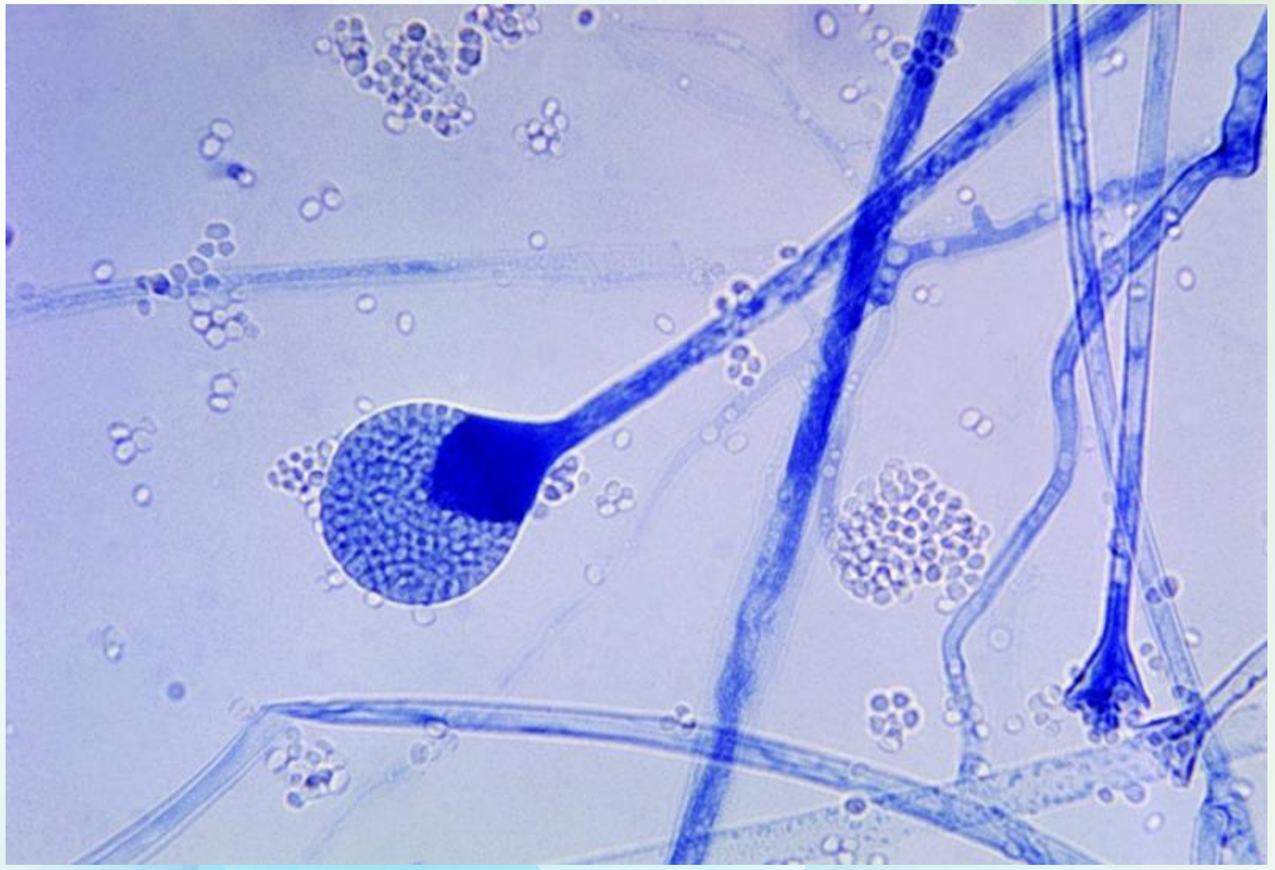
- Antibiotics – typically active against bacteria ONLY
- Mechanism—kill OR inhibit growth
- Resistance—evolutionary process caused by drug pressure selecting for resistant strains; overuse/misuse contributing factor
- Misuse—antibiotics are often prescribed for VIRAL infections and/or fungal infections



Fungi

- Can be single-celled or complex multi-celled organisms
- Ubiquitous but most live in soil or plant material
- 6 million species, more than 600 associated with humans

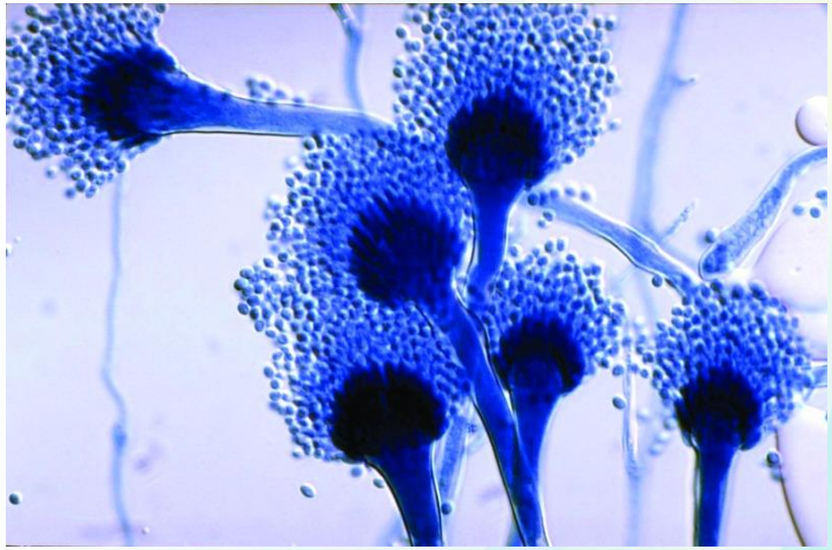
- Commensals (e.g. part of our microbiome)
- Pathogens (disease-producing, most often in immunocompromised hosts)

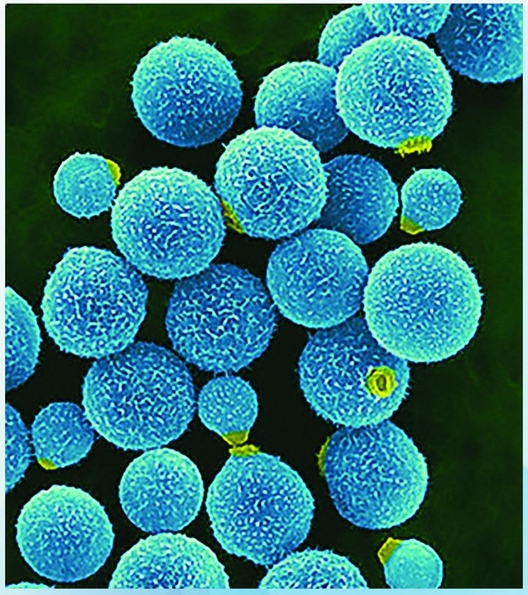


Fungi

- Sub-divided based on their life cycle:

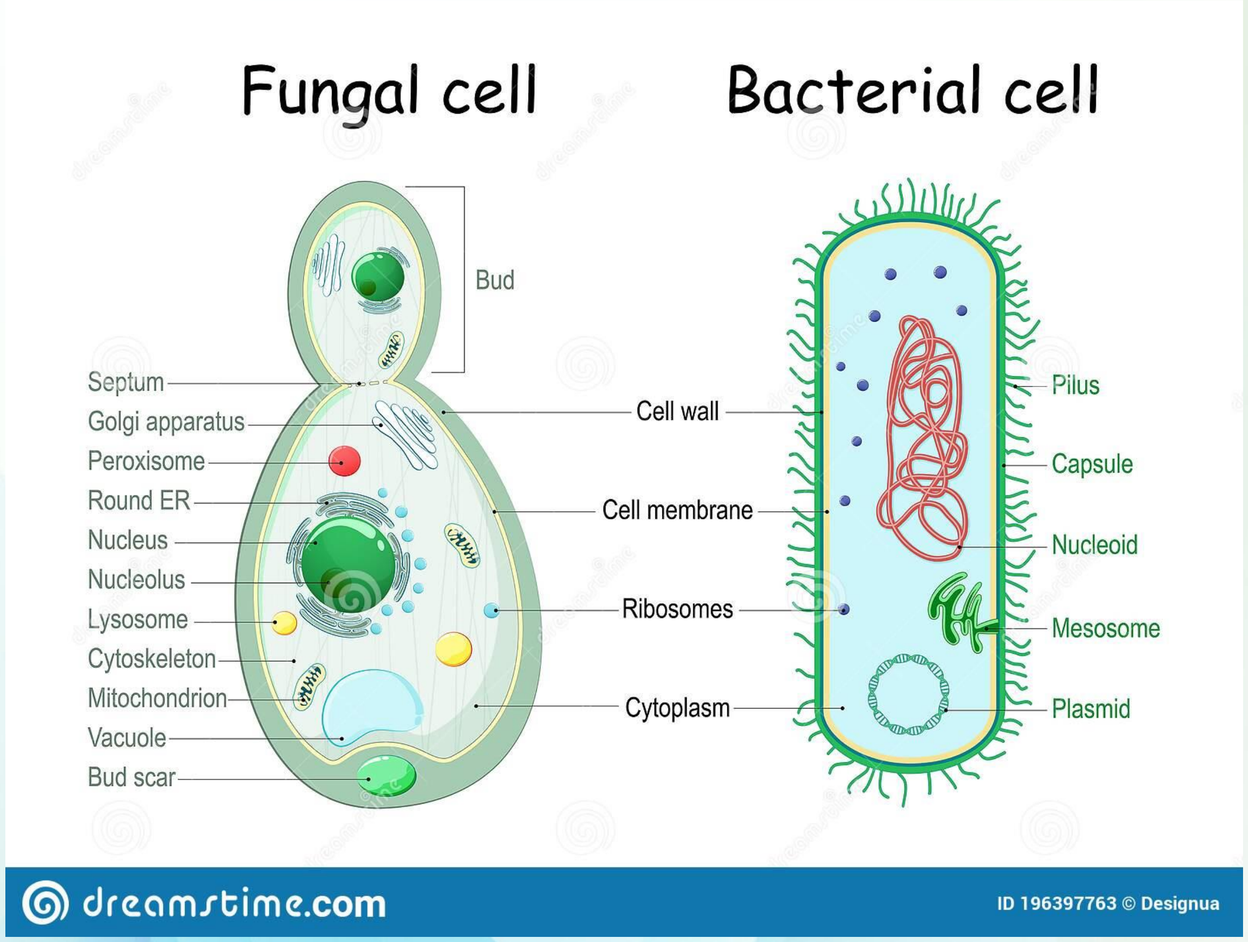
1. Multicellular filamentous molds
2. Single-celled microscopic yeasts
3. Macroscopic filamentous fungi (mushrooms)





Structure of Fungal Cell

- Cell wall and cell membrane provide structural rigidity and stability
- More complex than bacterial cell



Fungal Pathogens

Common

- Candida albicans (non-invasive), found on skin and in gut

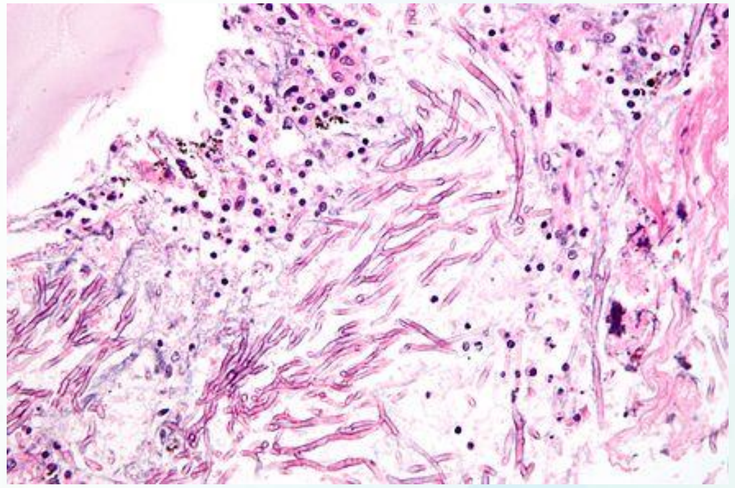
Associated with specific regions

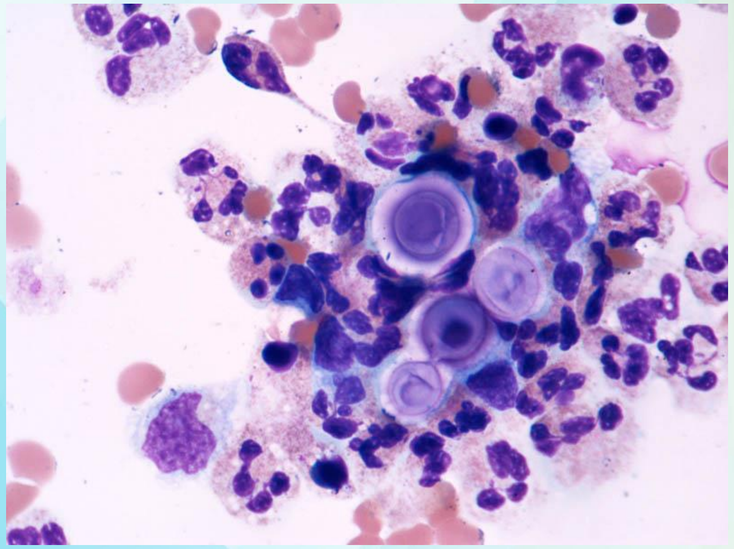
- Blastomycosis
- Coccidiomycosis
- Cryptococcus
- Histoplasmosis

Immunocompromised

- Aspergillus
- Candida spp (invasive)
- Mucormycosis

Many fungal infections are self-limited in immunocompetent host and are non-invasive



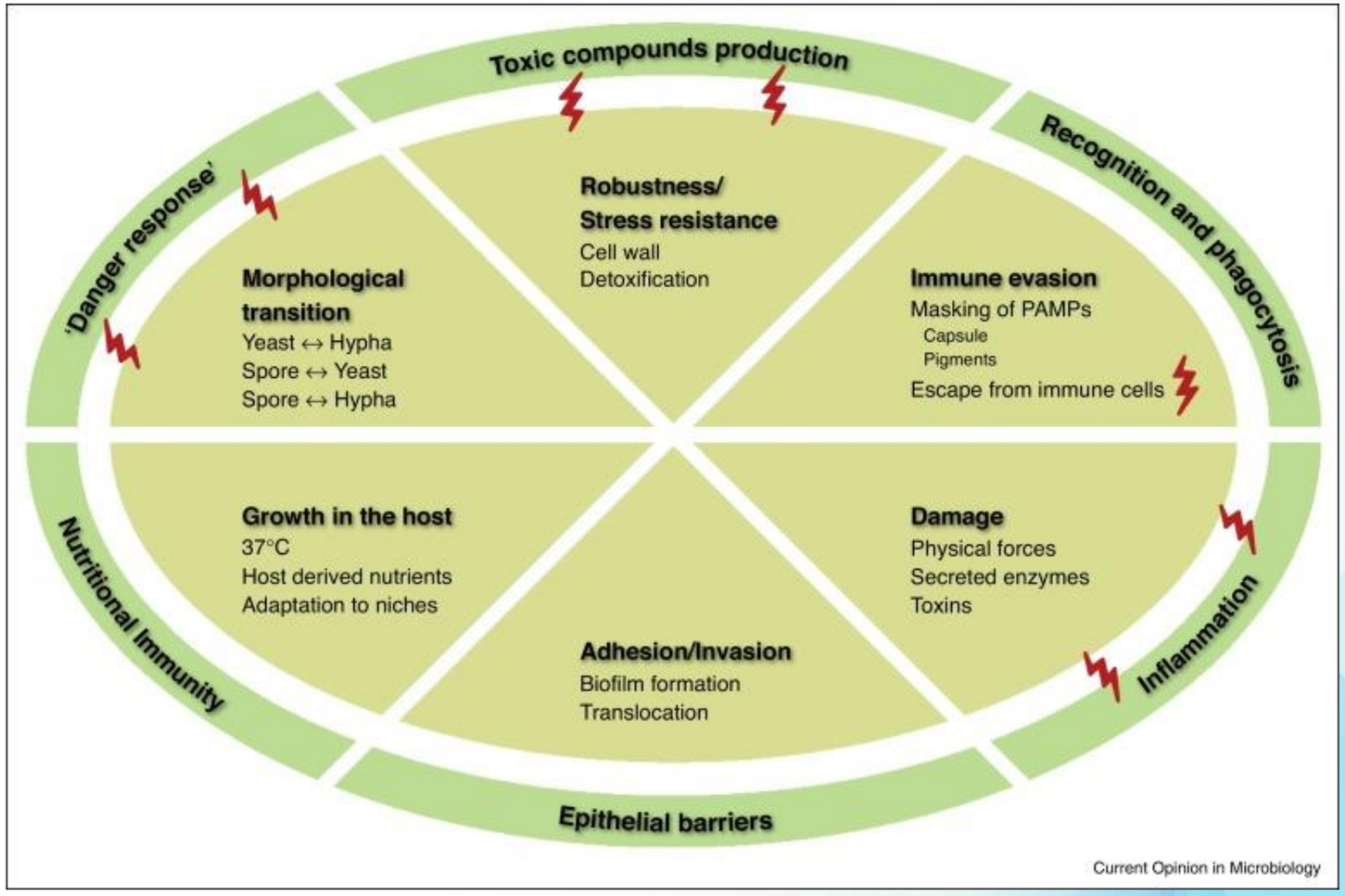


Fungal Eye Infections

- Candida species (in gut, skin, ubiquitous)
- Fusarium (lives in soil)
- Aspergillus (common fungus in environment)

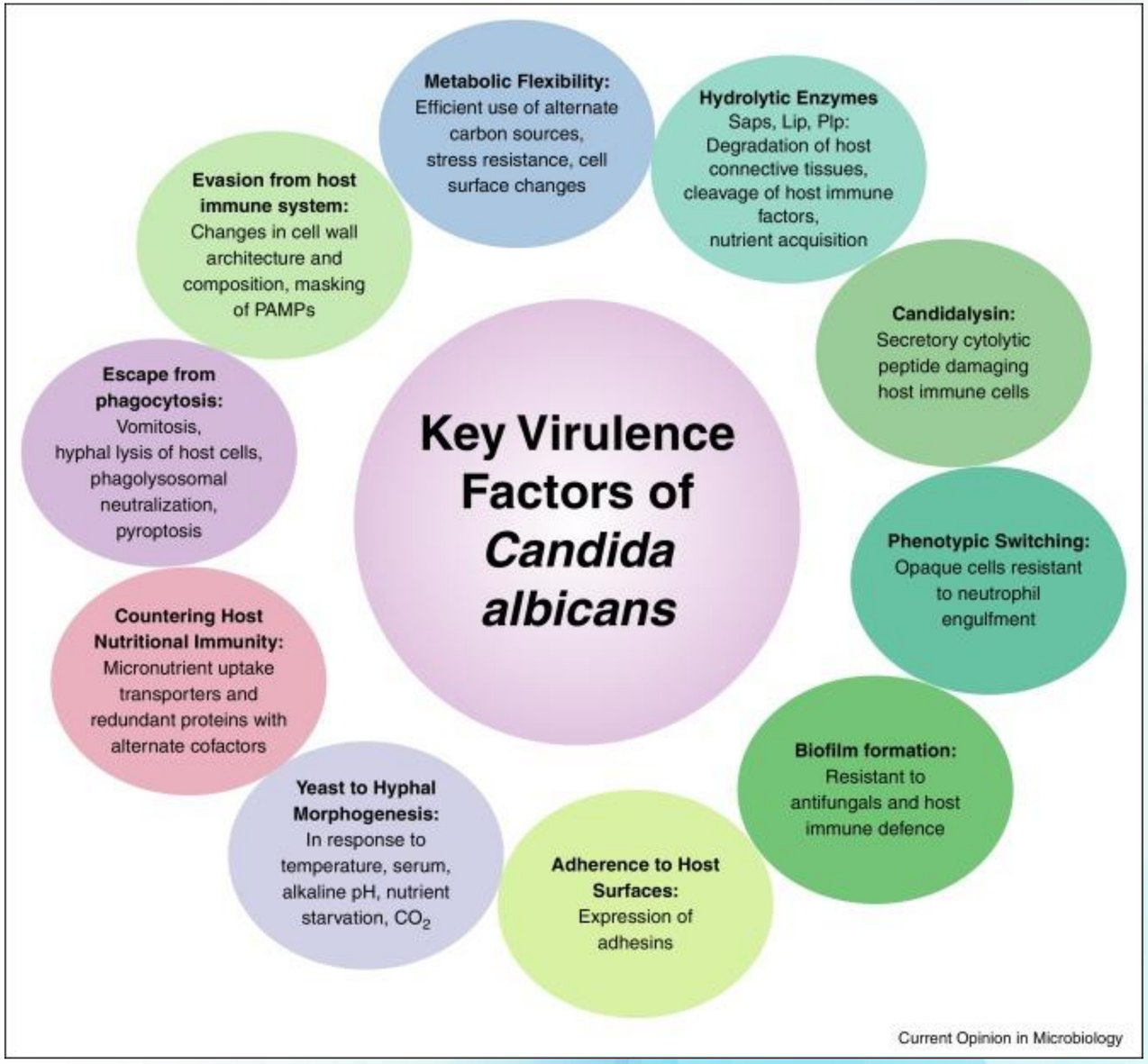
http://www.freestockphotos.biz/stockphoto/16349

FUNGAL VIRULENCE FACTORS



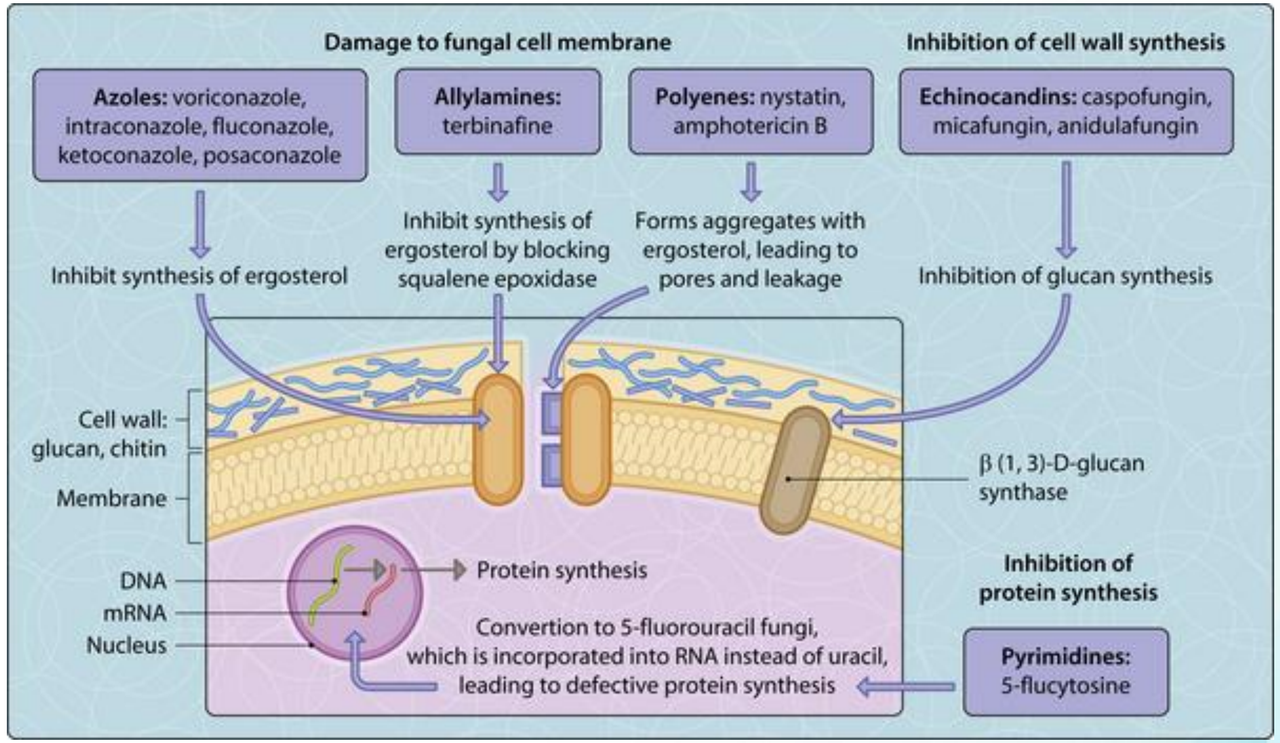
- Structural (cell wall)
- Morphological transition
- Adherence to surfaces
- Toxins
- Enzymes

https://www.sciencedirect.com/science/article/abs/pii/S1369527416300650?via%3Dihub



https://www.sciencedirect.com/science/article/pii/S1369527416301230?via%3Dihub

TREATMENT



- Damage cell membrane or inhibit cell wall synthesis
- Topical, oral, IV

Challenges:

- Eukaryotic animal cells and fungal cells share many of the same cell structures and targets—leads to severe side effects
- Resistance is common

https://musculoskeletalkey.com/antifungal-therapy/

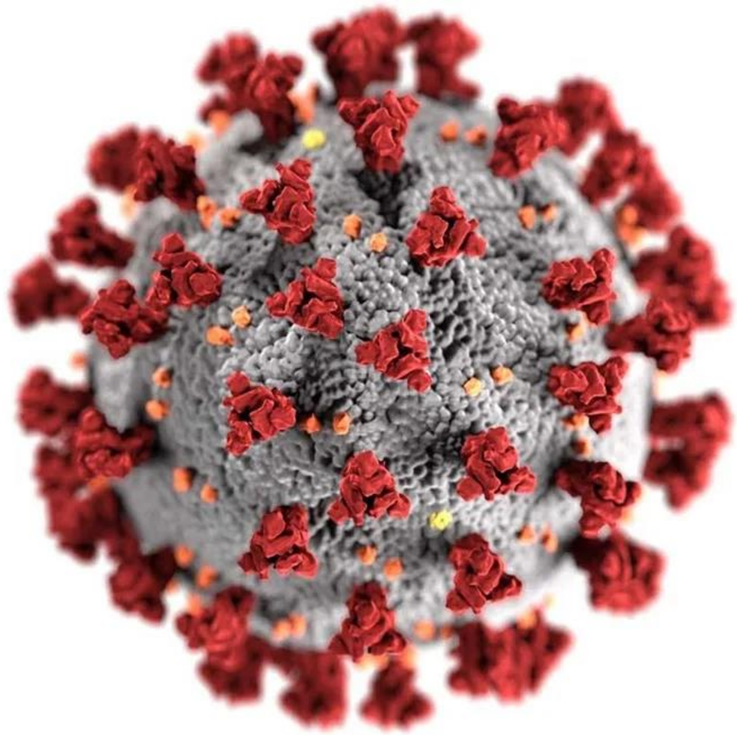
CANDIDA AURIS

- Species of genus Candida, grows as yeast
- First identified in 2009
- Multiple drug resistance
- Easily misidentified as other candida species
- Mortality with bloodstream infection due to C. auris 30%-60%

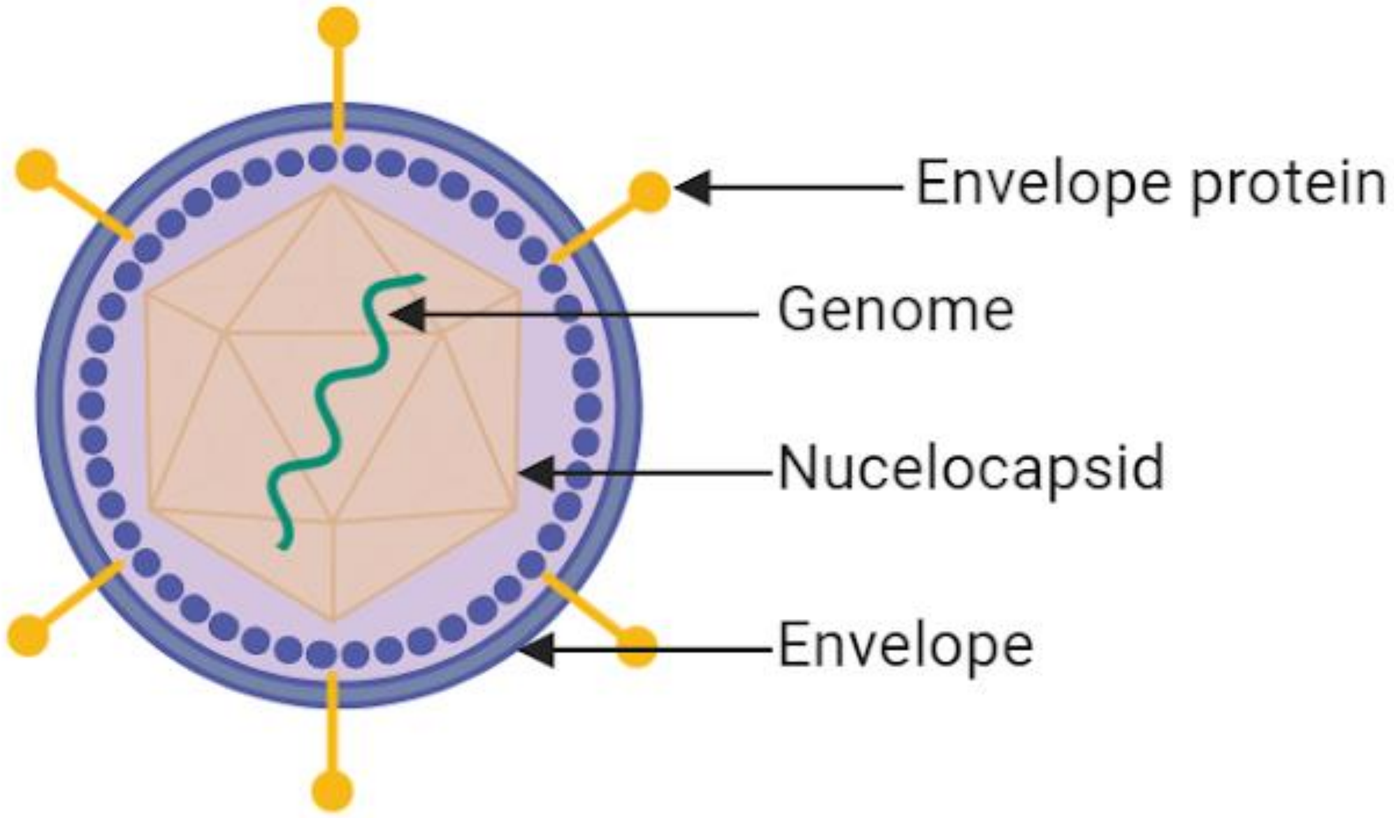
Casadevall A, Kontoyiannis DP, Robert V. On the Emergence of Candida auris: Climate Change, Azoles, Swamps, and Birds. mBio. 2019 Jul 23;10(4):e01397-19. doi: 10.1128/mBio.01397-19. PMID: 31337723; PMCID: PMC6650554.

Viruses

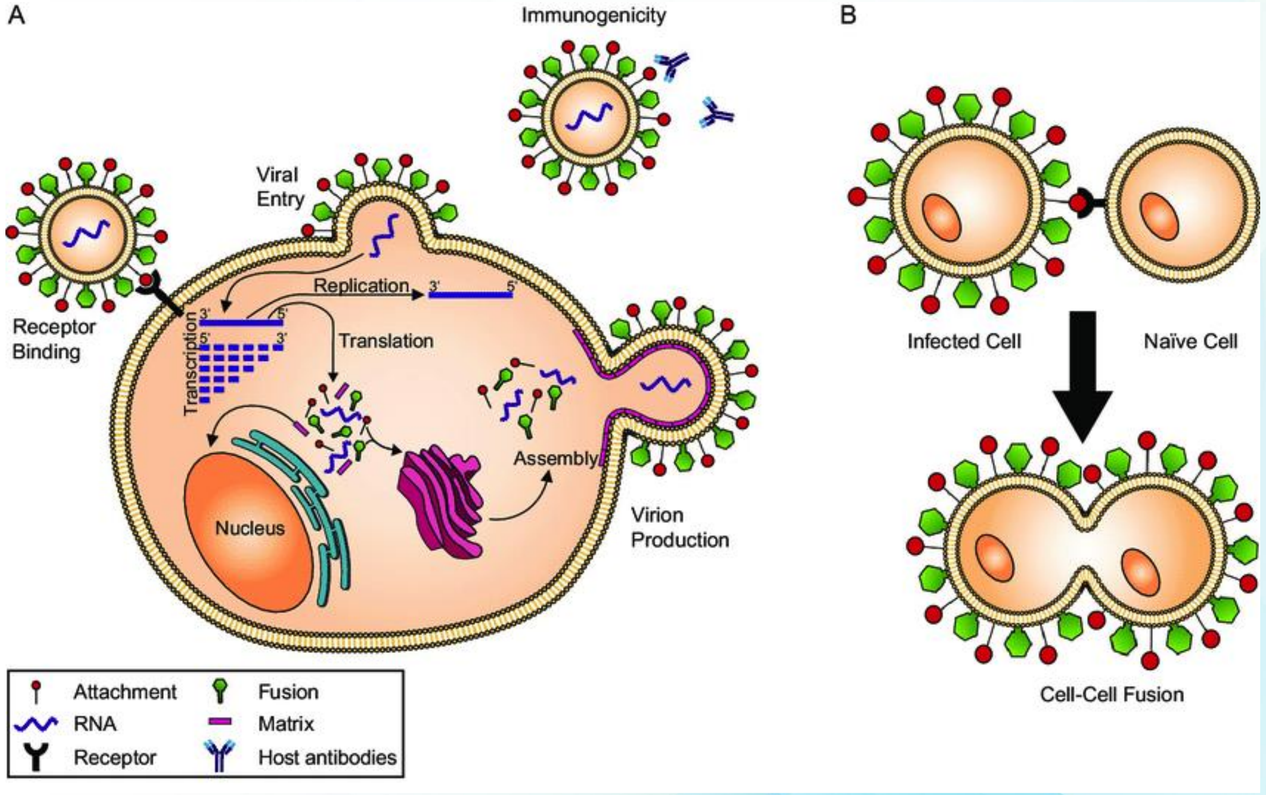
- Submicroscopic infectious particle that can only replicate in living cell
- Cannot exist outside of cell
- All contain nucleic acid (DNA or RNA), encodes unique genetic information
- Almost all have a shell (capsid)
- Most have other proteins
- Infect all life forms (plants, animals, bacteria)



VIRAL PARTICLE (VIRION)



VIRAL REPLICATION



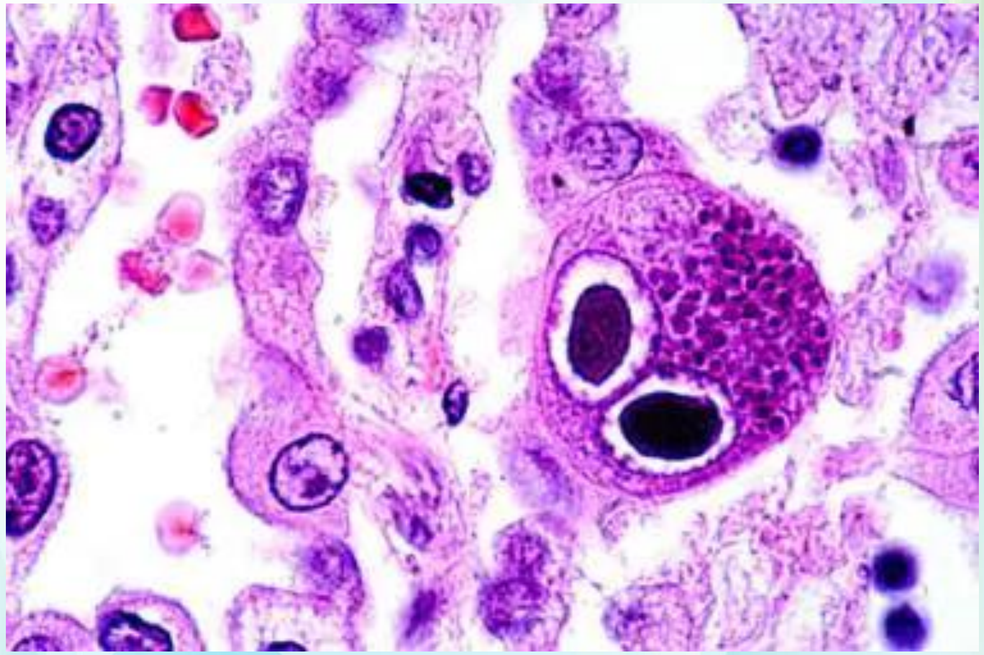
Ortega, Victoria & Stone, Jacquelyn & Contreras, Erik & Iorio, Ronald & Aguilar, Hector. (2018). Addicted to sugar: roles of glycans in the order Mononegavirales. Glycobiology. 29. 10.1093/glycob/cwy053.

VIRAL PATHOGENS/DISEASES

- Respiratory Viruses
  - Rhinovirus (one of the causes of common cold)
  - Influenza
  - SARS-CoV-2 (causes COVID)
  - Measles
- Emerging pathogens
  - Ebola
  - Mpox (formerly monkeypox)
- Zoonosis
  - Rabies
  - West Nile Virus
  - Yellow Fever
- Other
  - Chickenpox and shingles
  - Human Immunodeficiency Virus (HIV)
  - Cytomegalovirus (CMV)
  - Hepatitis (A, B, C)
  - Human Papillomavirus (HPV)

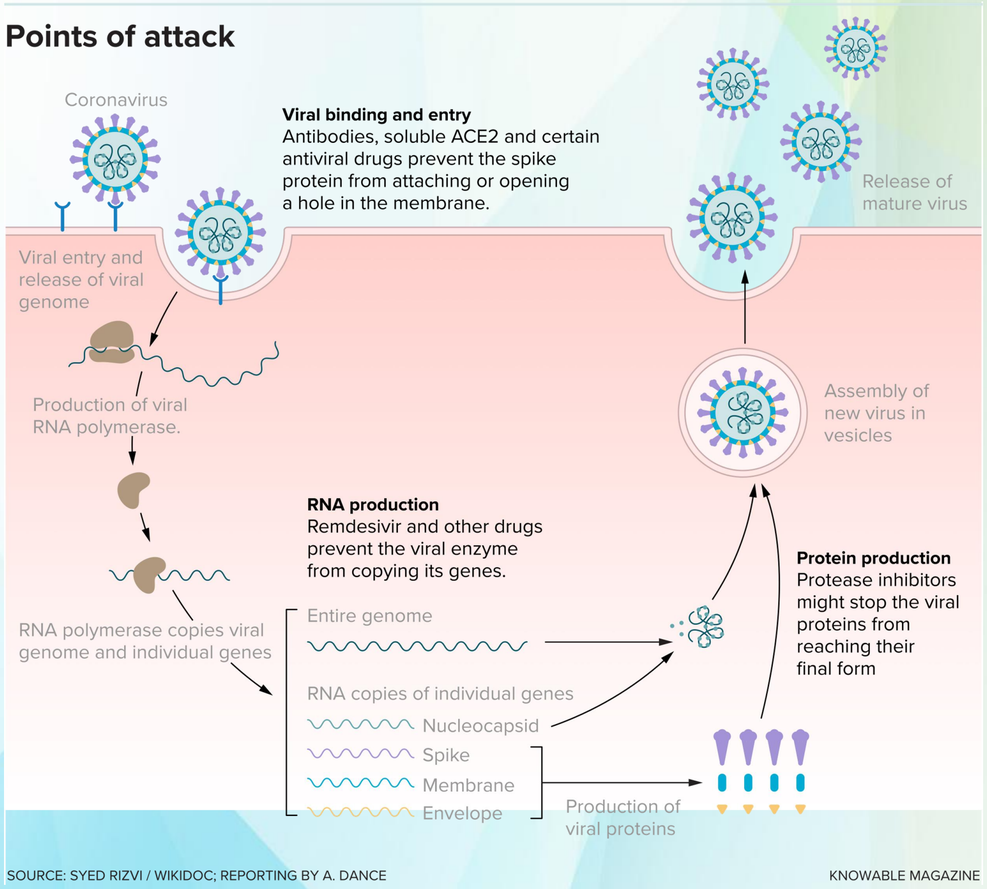
Ocular Viral Infections

- Human herpes viruses (HSV type 1 and HSV type 2)
- Cytomegalolovirus (CMV)
- Adenovirus



TREATMENT

- Antiviral medication available for some viral pathogens
- Mechanism: block any step in viral replication, sometimes multiple medications must be used (e.g. HIV) and suppress but do not eliminate the virus from the host
- Challenges:
  - Viruses rely on human cells to replicate—need to stop virus without damaging host cells
  - For acute viral illnesses, Must be delivered in early viral replication phase of illness
  - Viruses often replicate rapidly and mutate rapidly, enabling them to become resistance to medications



https://knowablemagazine.org/article/health-disease/2021/challenges-antiviral-treatments

Parasites

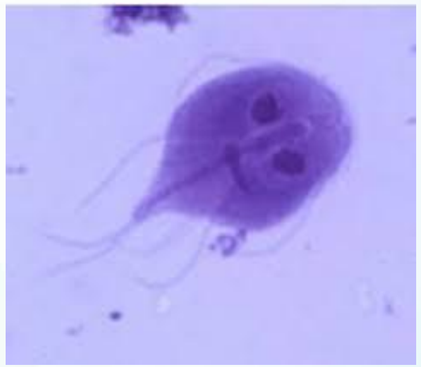
Organisms that lives on or in host organism

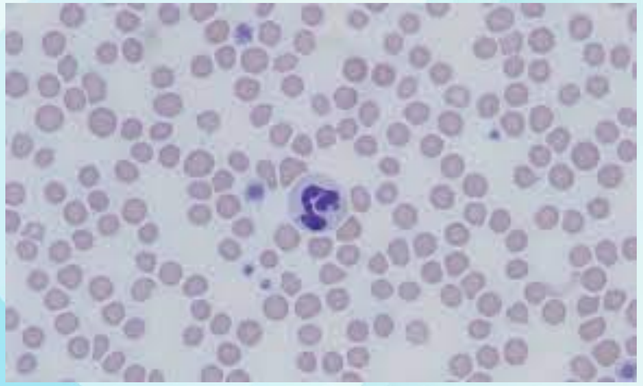
3 main classes:

1. Protozoa—microscopic, one-celled (e.g. giardia, malarial parasites)

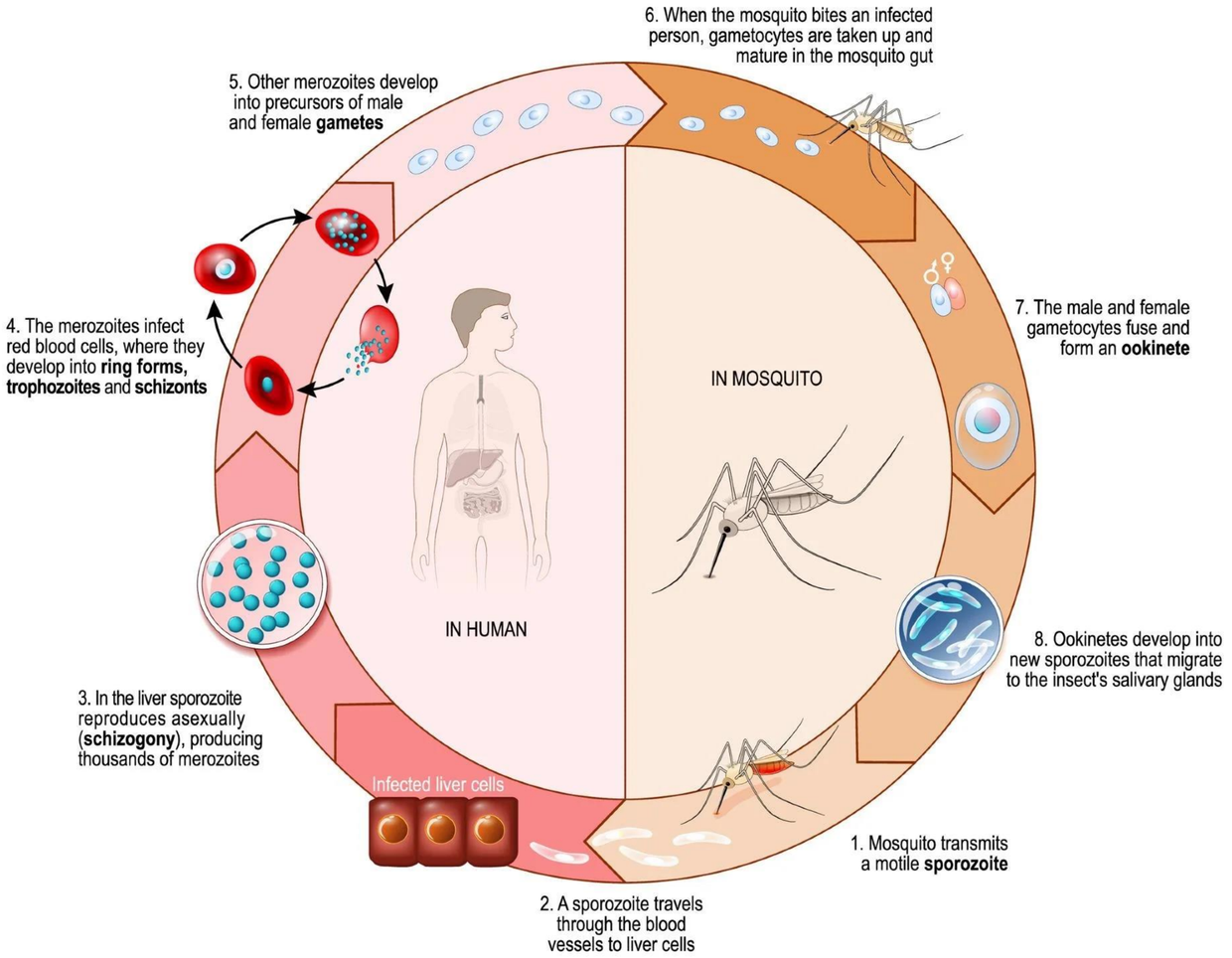
2. Helminths—large, multicellular, visible worms (e.g. flatworms)

3. Ectoparasite—large, multicellular (ticks, fleas, lice, mites). Also vectors for other pathogens





MALARIA LIFECYCLE



EYE BANK ASSOCIATION OF AMERICA®

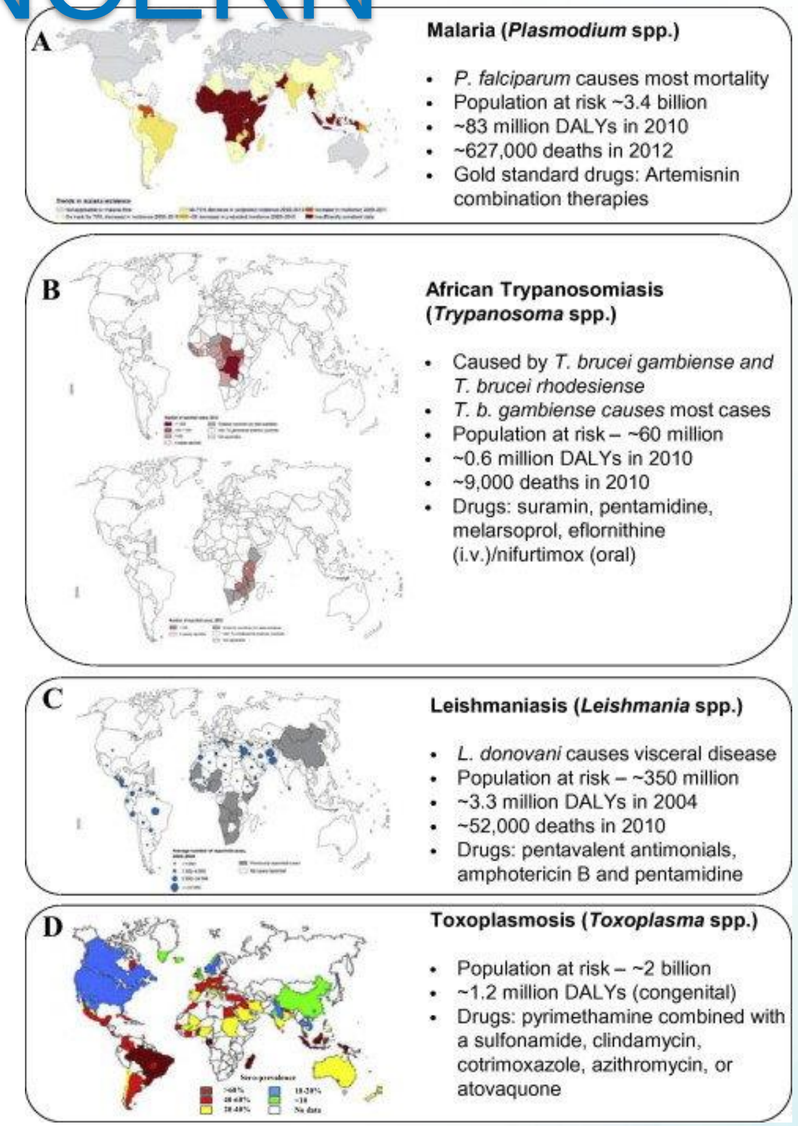
https://www.news-medical.net/life-sciences/The-Malaria-Parasite-Life-Cycle.aspx

Table 1. Worldwide Prevalence of Parasitic infections

Protozoa (P)/ Helminth (H): *Scientific Name*	Disease or Common Name	Estimated Worldwide Prevalence	Estimated Mortality Rank	Relative U.S. Prevalence
P: *Giardia lamblia*	Giardiasis ("beaver fever")	2-3 billion	Low	1-2 million per year
P: *Toxoplasma gondii*	Toxoplasmosis	1-2.5 billion	Very low	High rates of seroconversion but low rates of active infection[a]
H: *Ascaris lumbricoides*	Ascariasis (roundworm)	1 billion	Very low	Uncommon
H: *Necator americanus*	Hookworm disease	800-900 million	Very low	Somewhat, especially in the Southeast
P: *Trichomonas vaginalis*	Trichomoniasis	15% of women worldwide[b]	Very low	More dependent on sexual behavior than geographic location
P: *Entamoeba histolytica*	Amebiasis	200-400 million	No. 2	Low except in homosexual males, recent travelers, and immigrants
P: *Plasmodium* spp[c]	Malaria	200-300 million	No. 1	Recent travelers and immigrants only[d]
P: *Schistosoma mansoni*	Schistosomiasis	200-300 million	No. 3[e]	Uncommon
H: *Wuchereria bancrofti*	Filariasis[f] (roundworm)	200 million	Very low	Uncommon
H: *Taenia solium*[g]	Cysticercosis	>50 million	Low	May occur in those with poor hygiene and/or in contact with pigs
H: *Onchocerca volvulus*	Onchocerciasis ("river blindness")	37 million	Low, but high morbidity	Low in the U.S., but higher in Central and South America (highest in Africa)
P: *Trypanosoma* spp[h]	Chagas disease ("African sleeping sickness")	15-20 million	No. 3	Normally endemic in Central and South America, but increasing in the U.S.
P: *Leishmania* spp (many)	Leishmaniasis	12 million	No. 3	Uncommon, except in travelers, immigrants, and overseas military
H: *Enterobius vermicularis*	Enterobiasis (pinworm)	Common, no estimates	Very low	Common

[a] *Rates of positive serology in U.S. residents have been reported to be as high as 25% to 33% (and as low as 10%).*
[b] *The prevalence of trichomoniasis in women is better known because females exhibit more symptoms. Men are often asymptomatic or mildly symptomatic carriers and transmitters of disease.*
[c] *Treatment and prevention vary widely depending upon species and regional resistance patterns of* Plasmodium.
[d] *Malaria was once endemic in the U.S. To read about how it was eliminated, visit www.cdc.gov/malaria/about/history/elimination_us.html.*
[e] *The data are unclear regarding which infection is the third most mortal worldwide; it could be schistosomiasis, leishmaniasis (particularly the visceral and mucocutaneous presentations), or trypanosomiasis.*
[f] *Filariasis can be caused by several roundworm species that inhabit lymphatic and subcutaneous tissues, and many manifest as lymphatic filariasis or onchocerciasis ("river blindness").*
[g] Taenia solium *may cause intestinal tapeworm infection (taeniasis) that is typically acquired by undercooked infected pork. However, cysticercosis specifically is caused by the ingestion of fecal matter containing spores. This occurs via the oral-fecal route from someone currently infected by spore-releasing tapeworms.*
[h] Trypanosoma cruzi: *Chagas disease or American trypanosomiasis;* Trypanosoma brucei: *"African sleeping sickness."*
spp: species. Source: References 1, 3, 6, 12, 19.

EXAMPLES OF PARASITES OF CONCERN



- Malaria
- Toxoplasmosis
- Acanthamoeba
- Leishmania
- Chagas (T. cruzi)

Many have latent phase of disease, particular concern with immunosuppression

https://www.researchgate.net/figure/Distribution-and-disease-impact-of-major-human-diseases-caused-by-parasitic-protozoa_fig2_261029794

TREATMENT

Table 2. Antimalarial Drugs

Drug	Prevention Dosage	Treatment Dosage	Notes on Treatment	Notes on Prophylaxis[a]
Chloroquine	500 mg orally weekly	1 g orally initially, then 500 mg at 6, 24, and 48 h	Preferred over quinine for efficacy and toxicity reasons when *Plasmodium falciparum* is susceptible to chloroquine. Also preferred for *P vivax* or *P ovale* infections, followed by primaquine, if possible, to eradicate liver stages	For prevention, administer 2 doses (at a minimum, start 8 days before) prior to arrival in malarious area
Quinine	325 mg orally daily	~650 mg orally q8h for 7 days; consider use with doxycycline to shorten duration to 3 days	The basis of therapy in most chloroquine-resistant areas. Given IV (usually as quinidine) for severe malaria	Requires daily doses and long-term use for prevention, which increases toxicity. Other preventive drugs are usually preferred
Mefloquine	250 mg orally weekly	1,250 mg orally as a single dose	Susceptible strains can be treated with a large single dose. Effective against some chloroquine-resistant strains	Alternatively, can be given as a loading dose starting 4 days before traveling
Primaquine	30 mg orally (base)[b] daily; 1-2 days before departure and continue for 7 days after leaving malarious area	30 mg daily orally for 14 days to prevent relapse	First, a standard antimalarial is used to treat the acute malarial case (e.g., chloroquine). Then, primaquine is used if infection is caused by *P vivax* or *P ovale* to prevent relapse	Rarely used for primary prevention of malaria due to its toxicity and risk in G6PD-deficient patients. May be used for prevention of any malaria species but most logically in areas with *P vivax* or *P ovale*
Sulfadoxine-pyrimethamine	Not recommended for travelers. May be used for intermittent preventive therapy for at-risk patients	Usually a single oral dose: 50-75 mg pyrimethamine/1,000-1,500 mg sulfadoxine	Relatively slower acting than some other agents; therefore, not preferred for severe malaria	No longer recommended for prevention or treatment of *P falciparum* in most parts of Africa due to high rates of partial, if not full, resistance
Doxycycline	100 mg orally daily	100 mg orally twice daily; when used in combination with quinine the duration of quinine dosing may be shorted from 7 to 3 days	Not considered sufficient as monotherapy. Clindamycin may substitute for doxycycline in combination with quinine	Highly cost-effective for prophylaxis. Although used daily, should be continued for 4 wk after leaving area
Atovaquone-proguanil	1 tablet (250 mg/100 mg) orally once daily	4 tablets (total 1,000 mg/400 mg daily) for 3 days	Appropriate for chloroquine-resistant *P falciparum*, but rarely used for treatment	Primary use is for prophylaxis. It is uniquely sufficient to continue this agent for only 7 days after returning
Artemether-lumefantrine (U.S.) or artesunate-amodiaquine (outside U.S.)	Not routinely used for malaria prevention	Artemether-lumefantrine is available in a fixed-dose combination: 80 mg/360 mg, 6 oral doses over 3 days	Rarely are the artemisinin derivatives or amodiaquine used alone. In combination, they are highly effective against multidrug-resistant *P falciparum*	Not recommended

[a] Prophylaxis is usually 1 or 2 doses before departure and for up to several weeks after returning. For weekly prophylaxis, the drug must be started a minimum of 7-14 days before entering the malaria-endemic area. Daily prophylaxis may be started as late as 1-2 days prior. See prescribing information.
[b] A 26.3-mg tablet of primaquine phosphate is equal to a 15-mg primaquine base.
G6PD: glucose-6-phosphate dehydrogenase. Source: References 7-9.

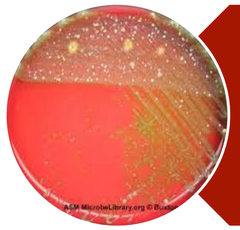
- Antiparasitics
- Antibiotics
- Anti-helminthic medication

Challenges:

- Life cycle of organism can be complex
- Resistance to medications (e.g. malaria treatment)

https://www.uspharmacist.com/article/drug-therapy-for-common-parasitic-infections-within-the-united-states

IDENTIFYING PATHOGENS



Bacteria

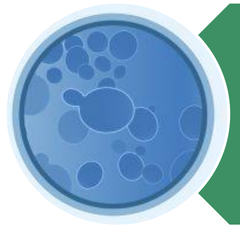
Culture (fluid or tissue)

Tissue histology

Virus

PCR

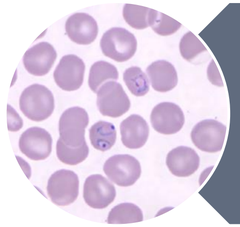
Histopathology (e.g. CMV)



Fungus

Culture

Histopathology

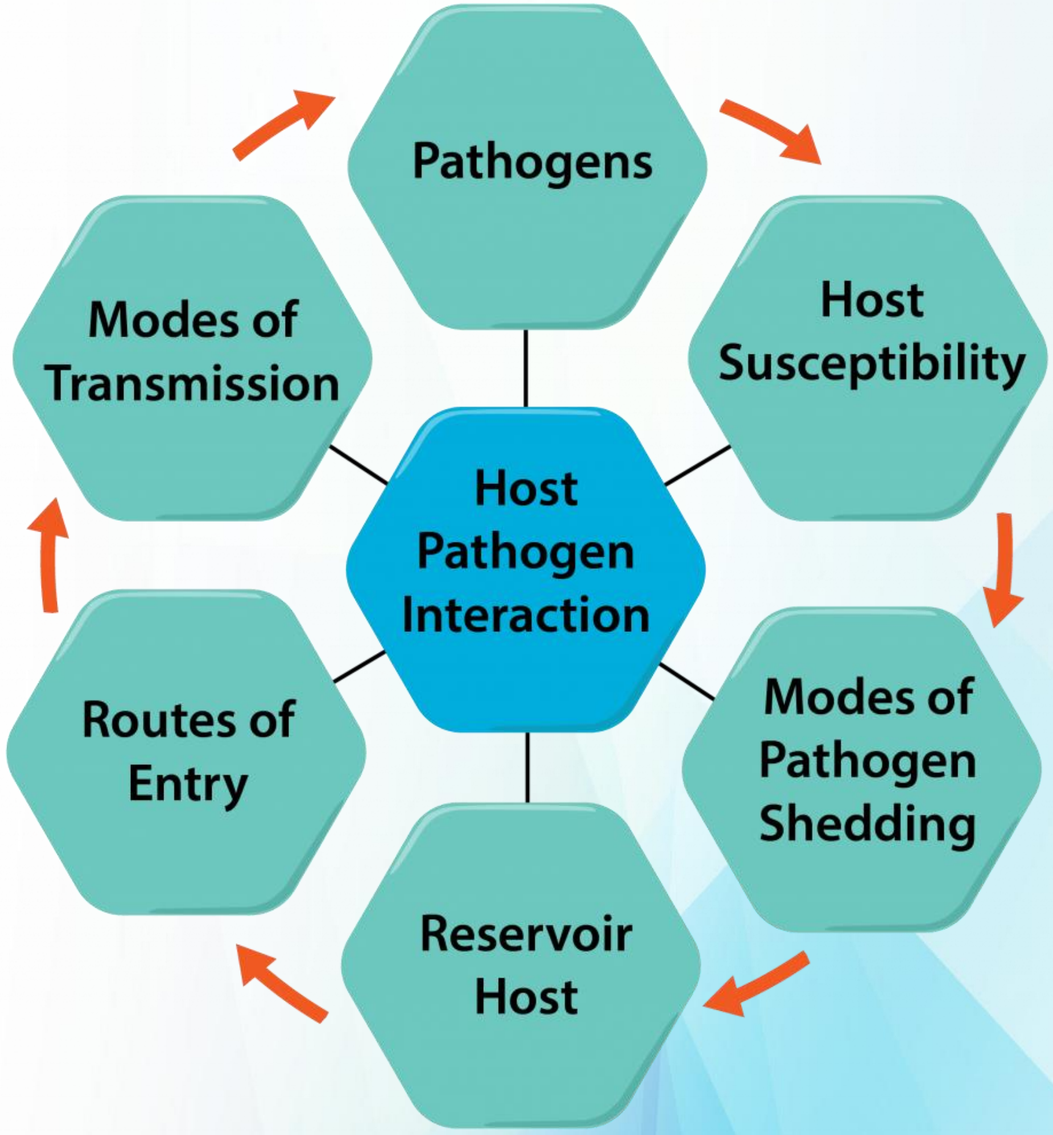


Parasite

Serology

Histopathology, microscopic examination of blood/fluid

MECHANISM OF INFECTION AND DISEASE



https://microbenotes.com/factors-affecting-bacterial-pathogenicity/

HOST BARRIERS TO INFECTION

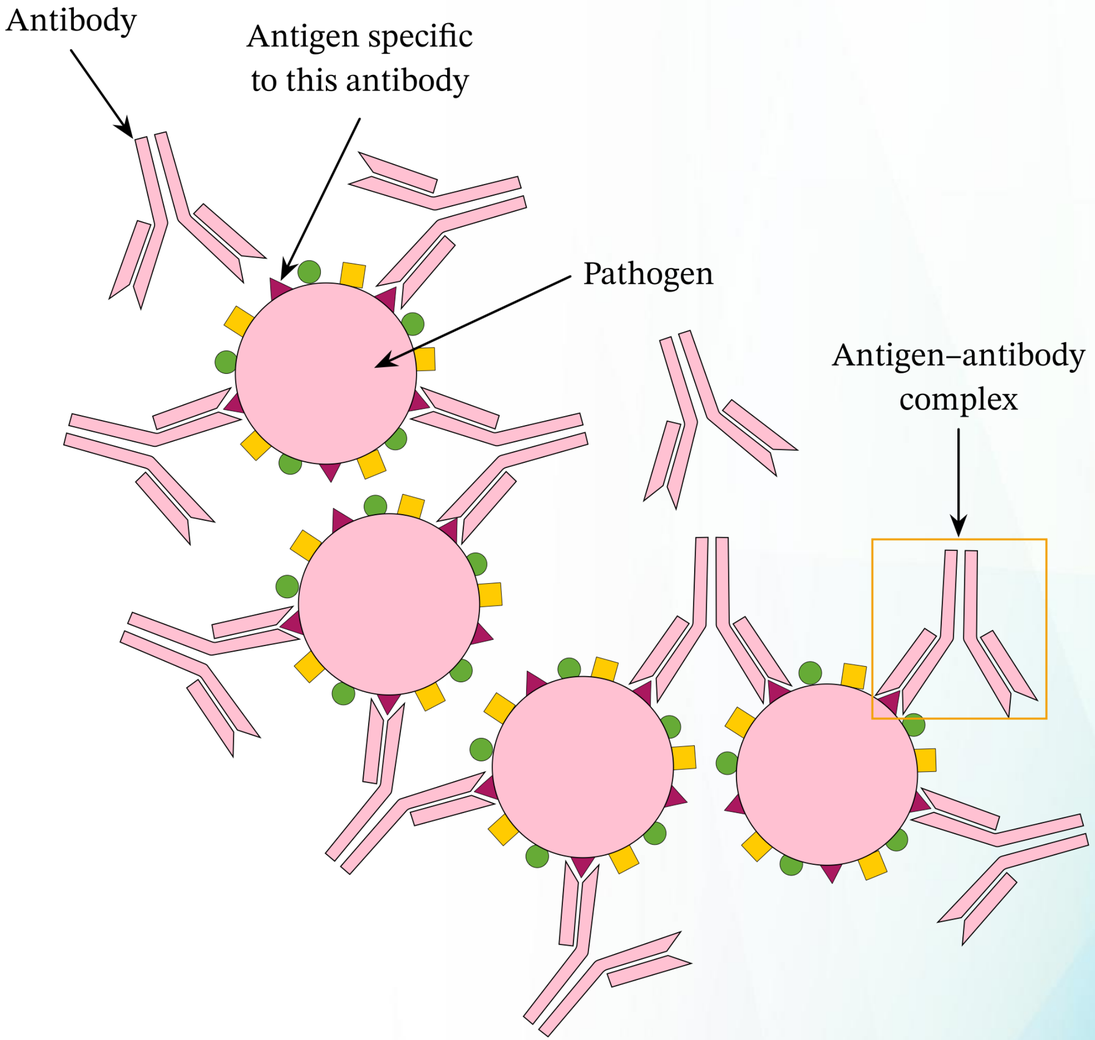
- Natural Barriers
  - Skin (if disrupted, microorganisms can enter) + cornea
  - Mucous membranes (tears, trapping action of mucus)
  - Respiratory tract
    - Upper airway filters (mucociliary epithelium)
  - Gastrointestinal tract
    - Acid pH of stomach
    - Antibacterial activity of pancreatic enzymes, bile, intestinal secretions
  - Bacteria on surface of skin, in GI tract

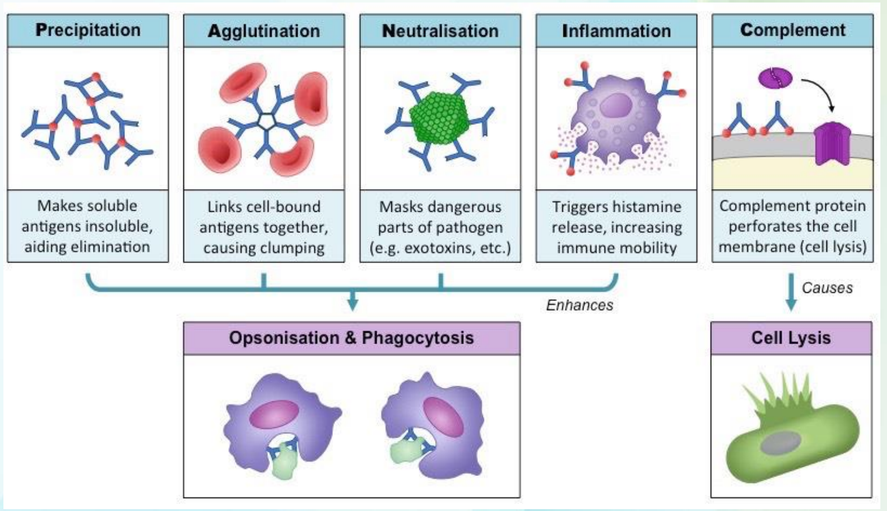
INNATE IMMUNITY

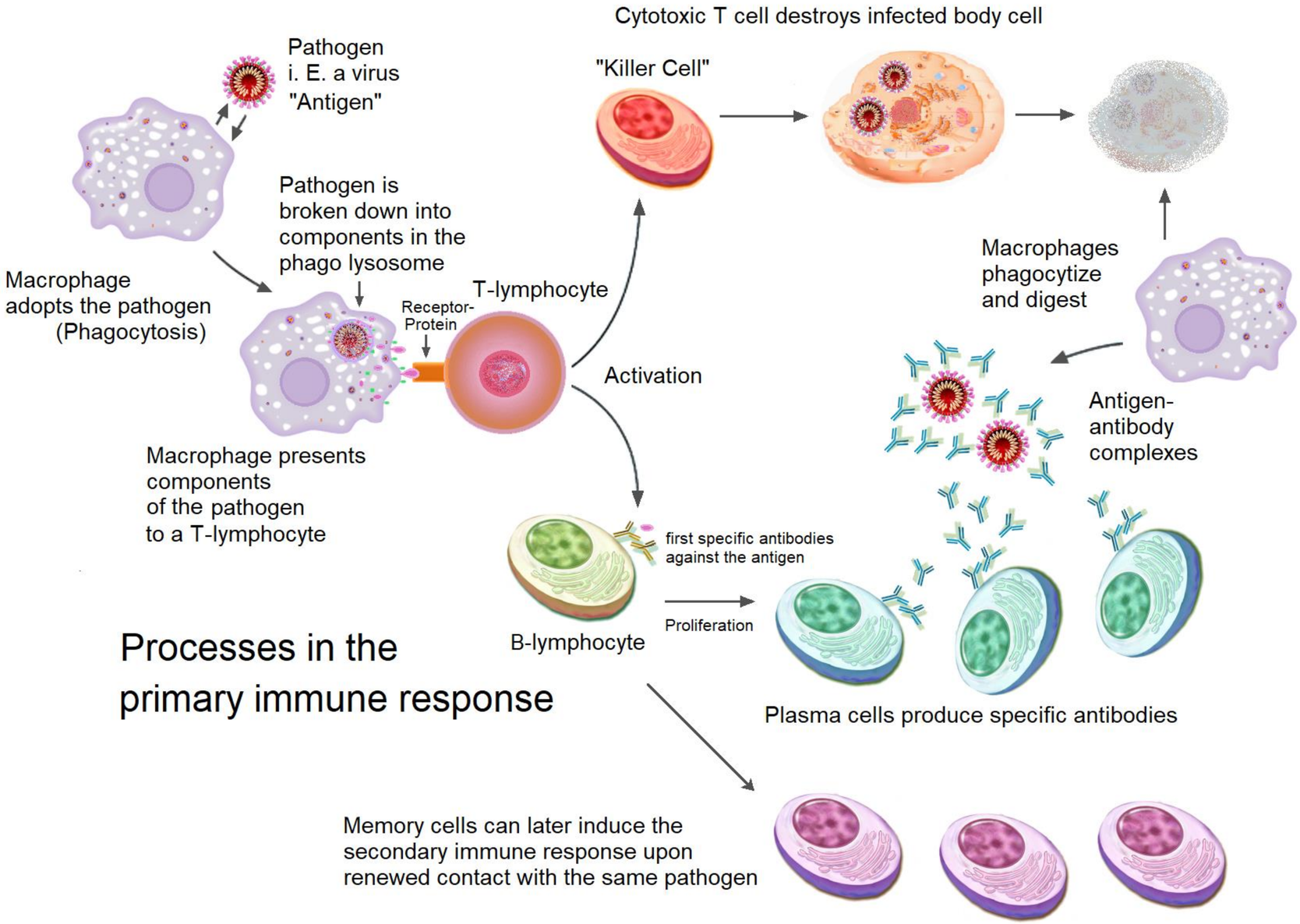
- Immediate, does not require prior exposure to pathogen
  - Macrophages phagocytize pathogen
  - Release of cytokines by macrophages (chemical signals)
    - Attract neutrophils
    - Initiate inflammation (cause swelling, fever, pain etc)
    - Initiate complement system which enhances killing of pathogens
- Activate the adaptive immune system

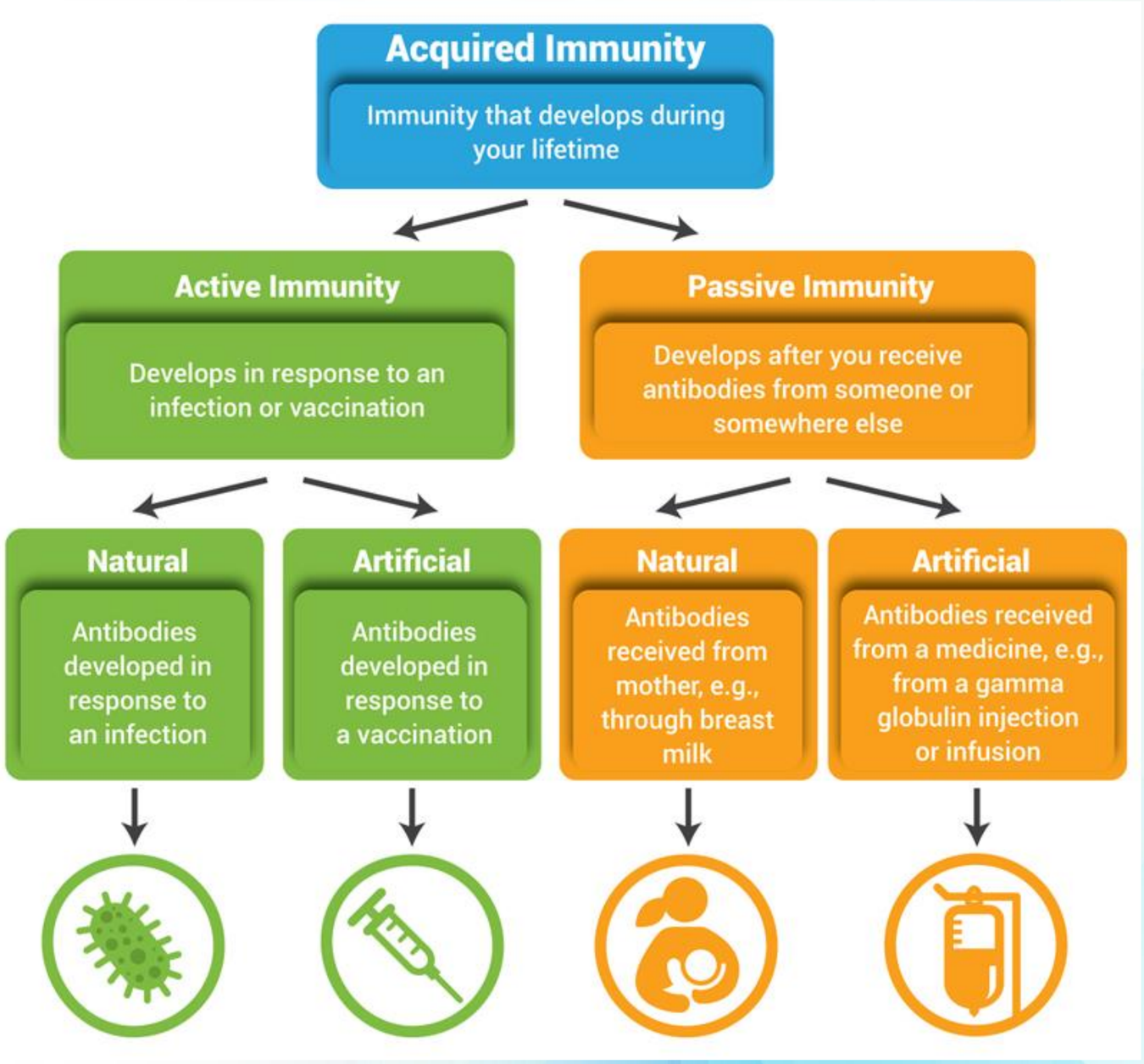
ADAPTIVE IMMUNITY

- Highly specific to particular pathogen that has previously been encountered
- Macrophage ingests pathogen and presents antigen
  - Antigen = molecular structure that is on surface of pathogen (can be protein, peptide, lipid, nucleic acid)
- Stimulates:
  - Humoral immunity (B-cells, antibodies specific to antigen + memory B-cells)
  - Cell-mediated immunity (T-cells)
- Creates immunological memory after an initial response to a pathogen
  - Memory B- and T-cells


Antibody
Antigen specific to this antibody
Pathogen
Antigen–antibody complex


Precipitation
Makes soluble antigens insoluble, aiding elimination
Agglutination
Links cell-bound antigens together, causing clumping
Neutralisation
Masks dangerous parts of pathogen (e.g. exotoxins, etc.)
Inflammation
Triggers histamine release, increasing immune mobility
Complement
Complement protein perforates the cell membrane (cell lysis)
Enhances
Causes
Opsonisation & Phagocytosis
Cell Lysis

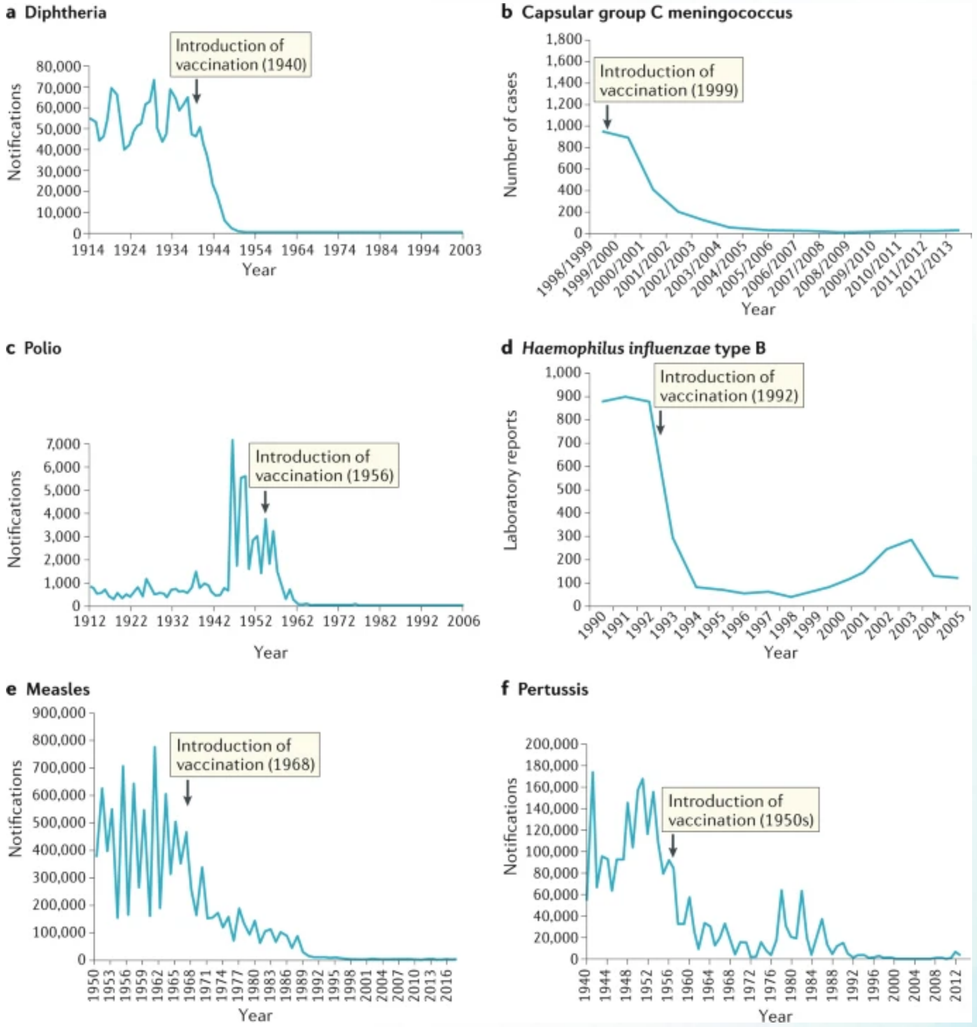




https://clinicalinfo.hiv.gov/en/glossary/acquired-immunity

VACCINES

VACCINES



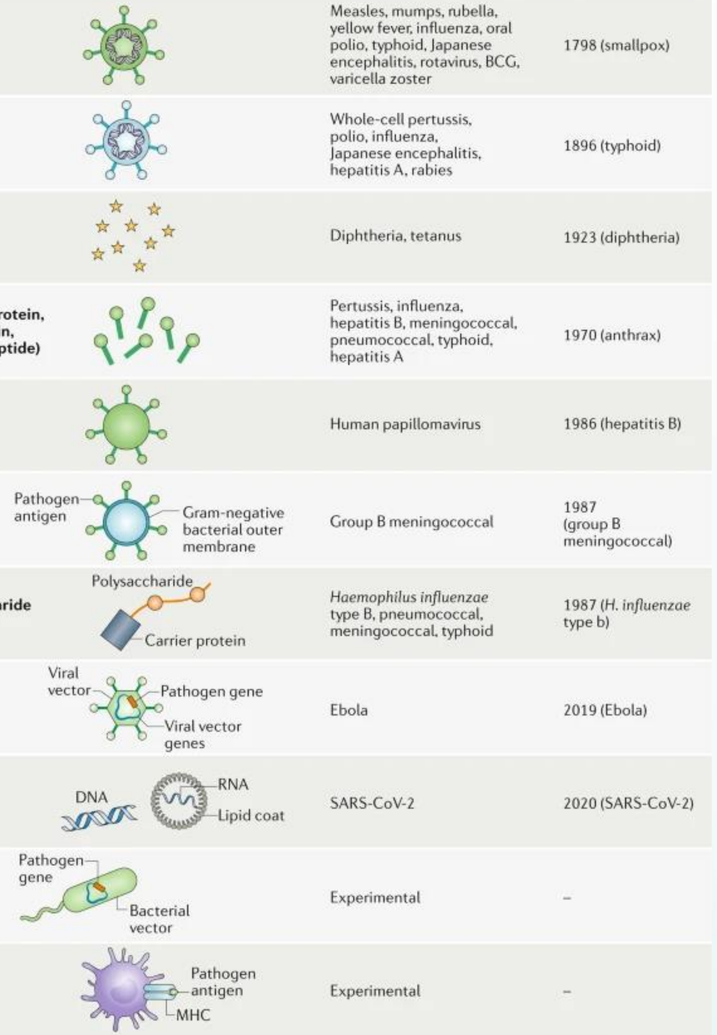
Definition:
Biological product that can be used to safely induce an immune response to confer protection against infection and/or exposure to pathogen

Essential component:
One or more protein or polysaccharide antigens that induce immune responses

Pollard, A.J., Bijker, E.M. A guide to vaccinology: from basic principles to new developments. *Nat Rev Immunol* **21**, 83–100 (2021). https://doi.org/10.1038/s41577-020-00479-7

VACCINE TECHNOLOGY

Type of vaccine	Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid	Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)	Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle	Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle	Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate	*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored	Ebola	2019 (Ebola)
Nucleic acid vaccine	SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored	Experimental	–
Antigen-presenting cell	Experimental	–



Classification

Live (attenuated)
Contains a weakened replicating strain of an organism

Inactivated
Contains only components of a pathogen or killed whole organisms

Subunit
Made from a piece of a pathogen, not the whole organism

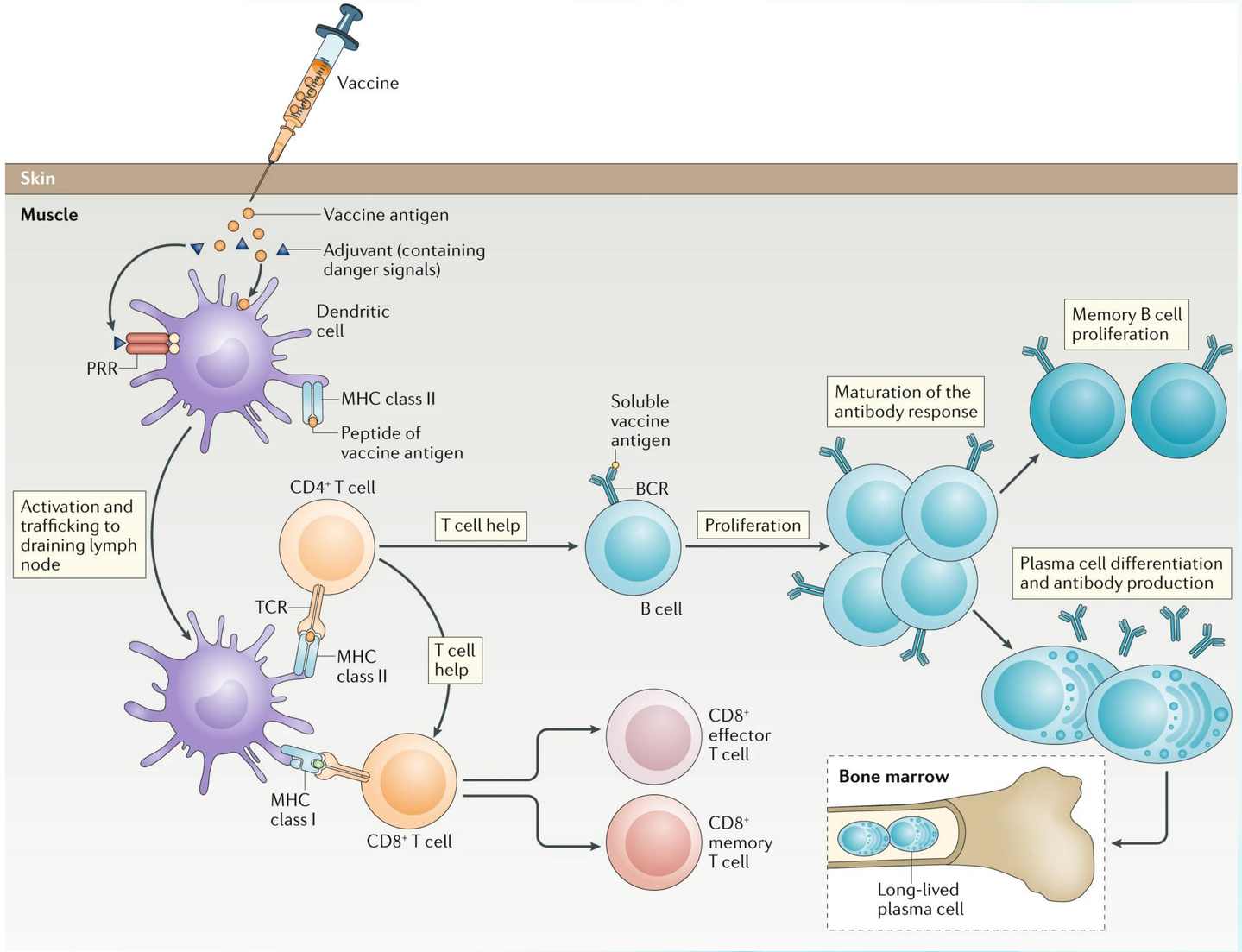
Viral vector
Uses harmless virus to deliver to the host cells the genetic code of the antigen

Toxoid
Uses inactivated toxins to target toxic activity created by bacteria

mRNA
Uses mRNA (genetic material) that “teaches” our cells to make a harmless piece of the pathogen and triggers and immune response

Adjuvant: can be added to inactivated vaccines to improved immunogenicity of the vaccine

Pollard, A.J., Bijker, E.M. A guide to vaccinology: from basic principles to new developments. *Nat Rev Immunol* **21**, 83–100 (2021). https://doi.org/10.1038/s41577-020-00479-7



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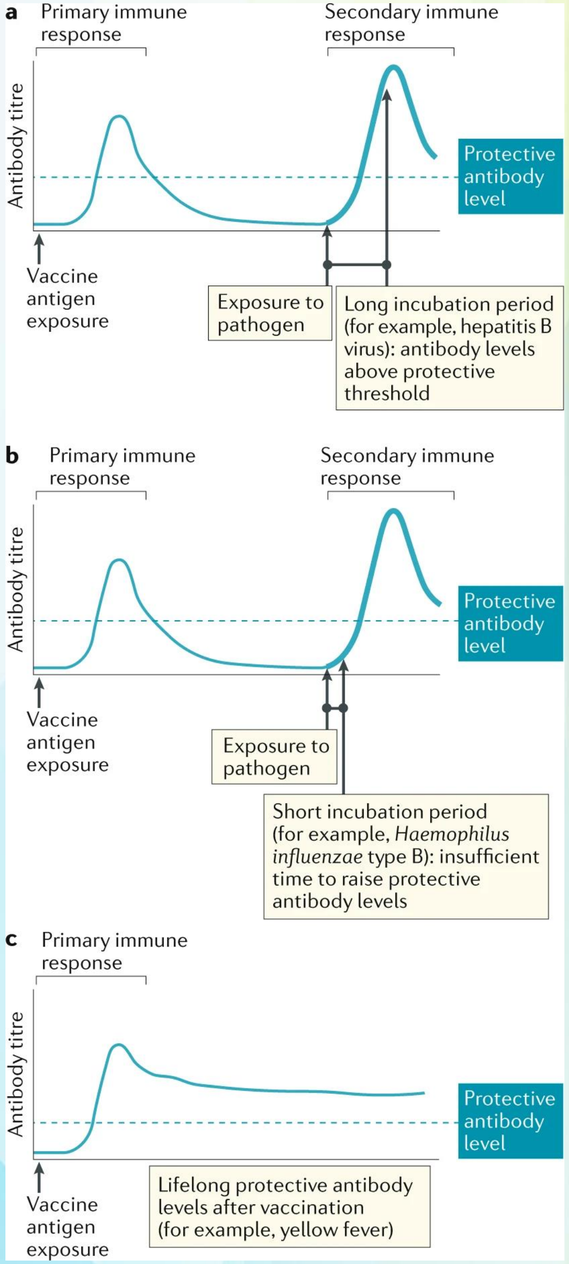
Longevity of Protection

- Antibody levels wane over time
- Interplay between time of re-exposure, incubation of pathogen, rapidity of memory cell response
- Prevention of infection vs disease



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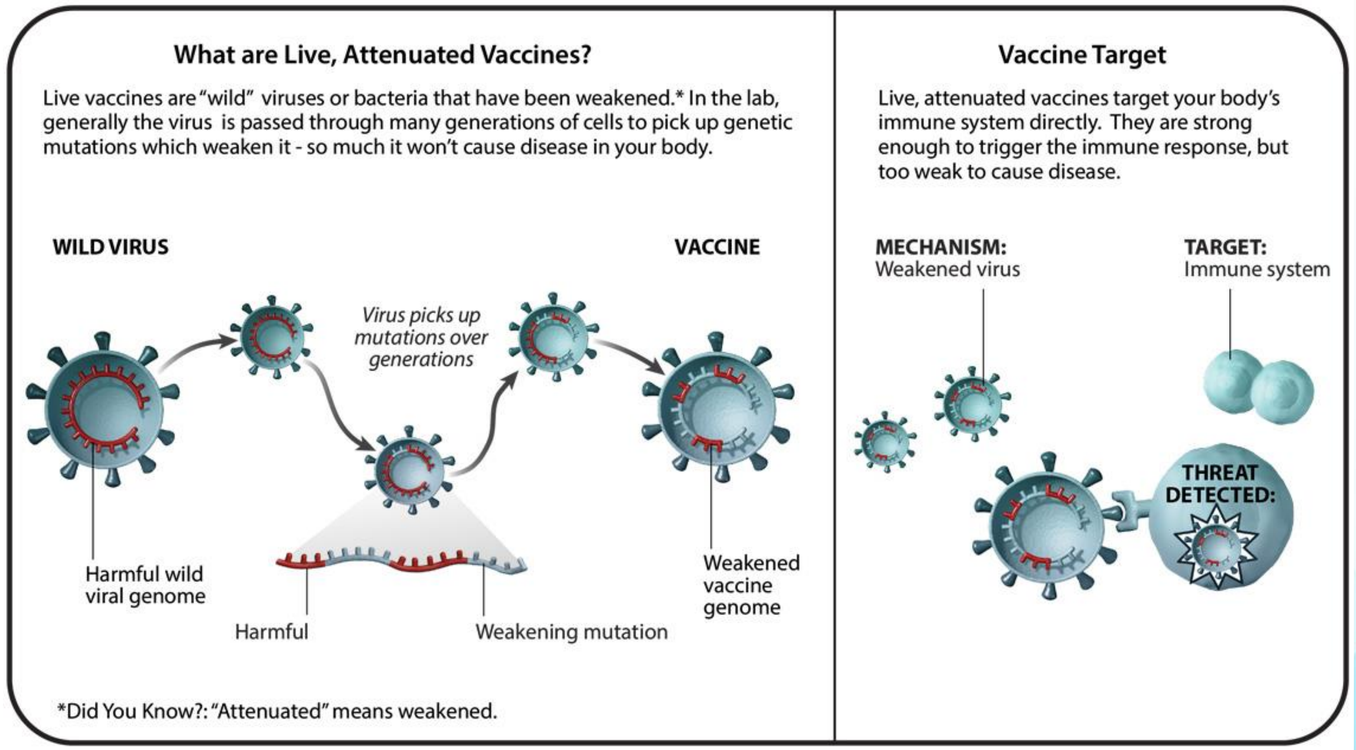
LIVE VACCINES



Examples:

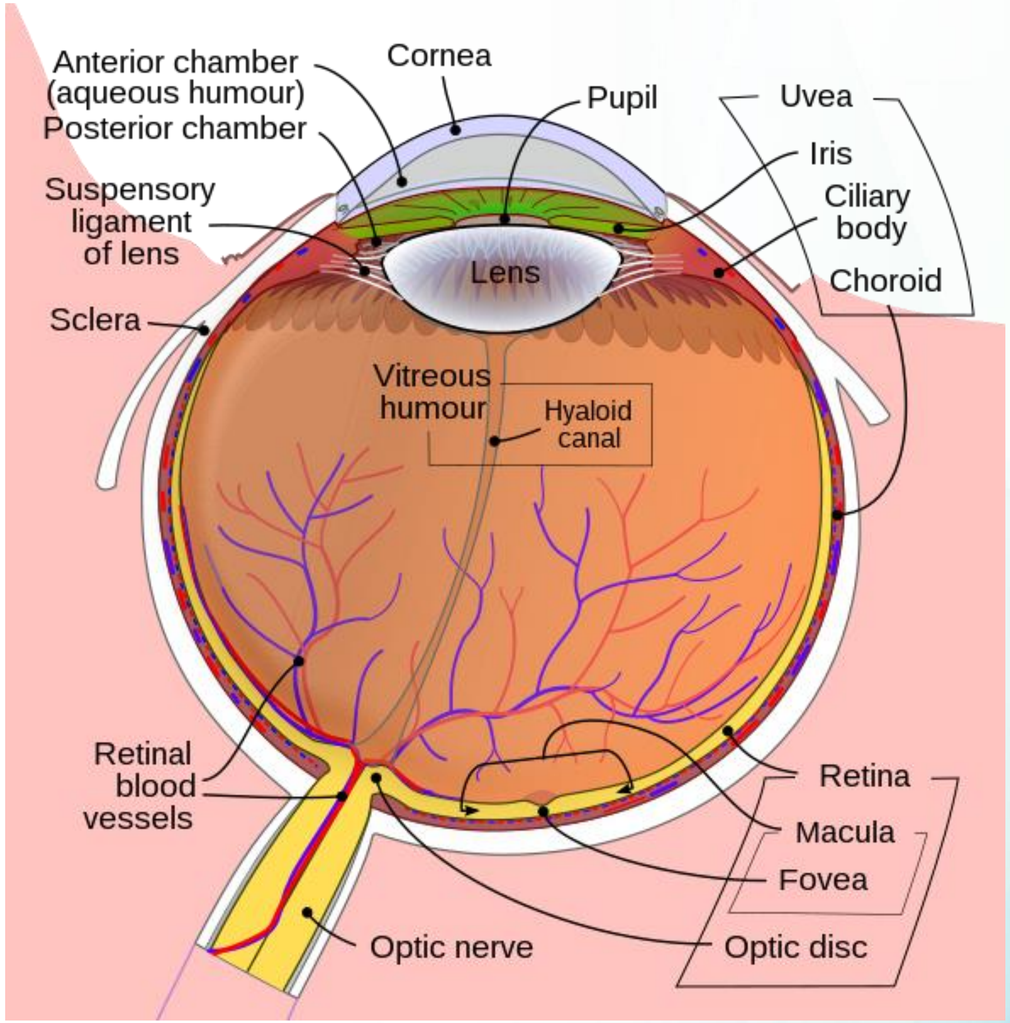
- MMR (measles, mumps, rubella)
- Yellow Fever vaccine
- Oral polio

Risk of live vaccines:

- Benign in most patients
- In immunocompromised individuals, risk of reversion to virulence
- *Contraindicated in certain populations, including solid organ transplant (receiving systemic immunosuppression)*

CORNEAL TRANSPLANT

CORNEA



Mechanisms of immune privilege:

1. Lack of vascular supply in lens and central cornea prevents innate and adaptive immune system from interfering
2. Vascular barrier in the eye helps keep clear from inflammation
3. 90% aqueous humor does not drain to lymph nodes
4. Scarcity of antigen presenting cells (less inflammation)

INFECTION RISK CORNEAL TRANSPLANT

- Risk of graft rejection
  - 2 year survival > 90%, but 25-70% in recipients with high-risk factors for rejection
- Causes of rejection/graft failure:
  - Immune rejection (immunologic response to graft)
  - Infection

EYE BANK ASSOCIATION OF AMERICA®

https://www.ncbi.nlm.nih.gov/books/NBK519043/

POST-TRANSPLANT INFECTION RISK

Solid Organ

- Highest risk due to immunosuppression of recipients and vascularization of organs

Tissue

- Lower risk may reflect host's normal inflammatory and immune function as well as graft disinfection with tissue allografts

Cornea

- Lowest risk due to fact that cornea is avascular and recipients not usually immunosuppressed

CORNEAL TRANSPLANT INFECTIONS

- Important source of post-transplant infection is donor tissue
- Potential consequences transmitted infection:
  - Endophthalmitis
  - Graft rejection
  - Loss of vision
  - Systemic illness

EBAA GUIDELINES ON COMMUNICABLE DISEASES

The following communicable diseases and disease agents are relevant for ocular tissue (§ 1271.3(r)(1)(i)):

i. Human immunodeficiency virus (HIV), types 1 and 2;

ii. Hepatitis B virus (HBV);

iii. Hepatitis C virus (HCV);

iv. Human transmissible spongiform encephalopathy (TSE); including Creutzfeldt-Jakob disease (CJD); and

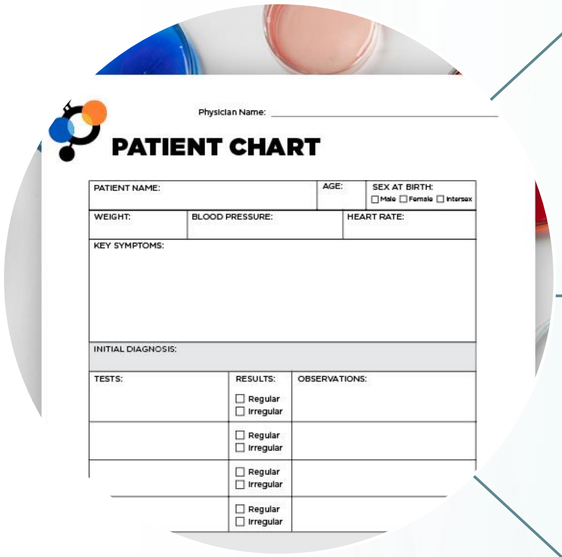
v. Treponema pallidum (syphilis)

EBAA GUIDELINES ON COMMUNICABLE DISEASES

II. A communicable disease agent or disease meeting the criteria described in § 1271.3(r)(2), but not specifically listed in § 1271.3(r)(1), is relevant if it is one:

- For which there may be a risk of transmission by ocular tissue
- That could be fatal or life-threatening
- For which appropriate screening measures have been developed
- Examples of RCDADs not specifically listed in § 1271.3(r)(1) as relevant include, but are not limited to:
  - West Nile Virus
  - Sepsis
  - Vaccinia
  - Zika Virus

CHART REVIEW



Systemic Symptoms

- Fevers
- Hemodynamic instability

Positive cultures (bacteria, fungus)

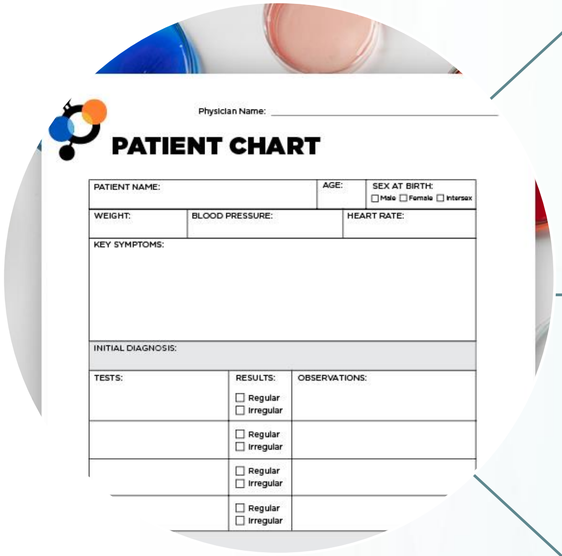
- Growth in a normally sterile site (e.g. blood, urine, CSF)
- Colonization vs infection

Viral data

Parasite data

- PCR
- Serology
- Tissue pathology

CHART REVIEW



History

- Travel history
- Other important medical history

Hospital course

- Antibiotic/antifungal treatment
- Sepsis
- Repeat blood cultures?

Cause of death

- What role (if any) did infection play?

CHART REVIEW

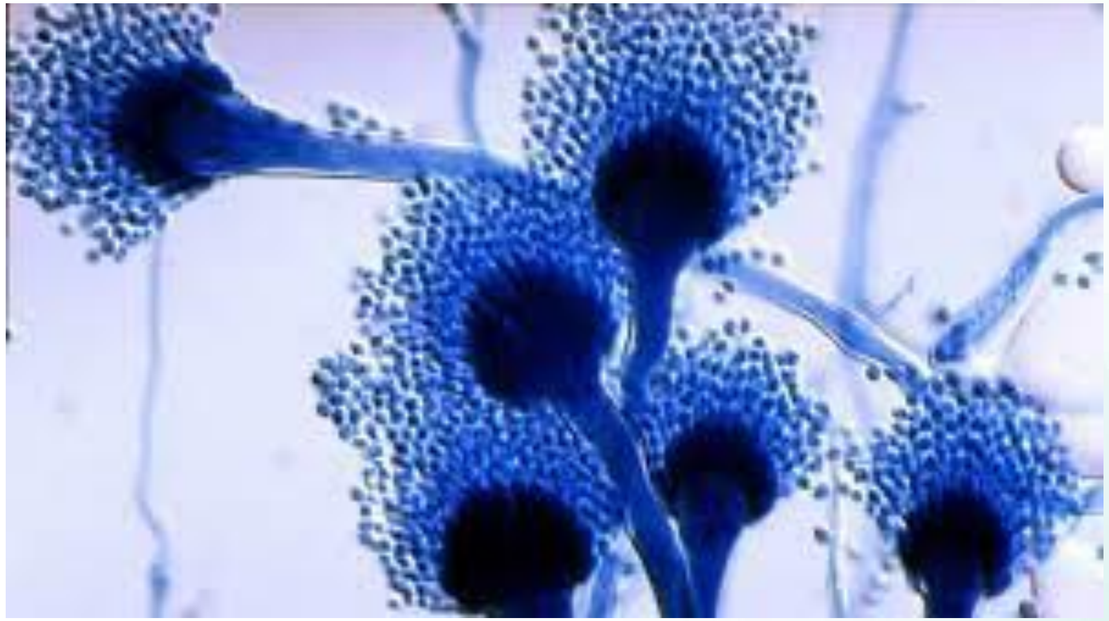
Organism of Concern per EBAA	Example: West Nile Virus, Hepatitis B virus	Reject
Colonization or treated/cleared infection	Example: repeat blood cultures negative	Possibly accept
Evidence of disseminated or difficult to treat infection	Example: sepsis, repeat cultures positive, untreated infection	Reject

CONCLUSIONS

- Infection rates low in corneal transplant but still a risk

- Understanding range of pathogens, virulence, immune system responses, and treatment can help guide chart review when looking for suitable donors

QUESTIONS



Thank you

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