Review Summary – PH260A

INTRODUCTION:
Framework: Each disease has a:

1. Etiology – Why does the disease occur? What did it originate from?
2. Epidemiology – How does a disease distribute?
    a. Occurrence – Hof oten does it occur (incident or prevalent -> new vs total)
    b. Reservoir – Where does it stay stable?
    c. Transmission – how does it spread? (Mechanism)
    d. Temporal pattern (self exp)
    e. Communicability – Whne does the infected spread disease? What stage?
3. Pathogenesis: How does the infection lead to disease
4. Clinical: What can we see in the clinic?
5. Diagnosis: What specific tests can we run to check this disease
6. Treatment: What can we do to treat the disease?
7. Prevention: Given all of the above, how can we prevent disease spread?

Symbiosis: The relationship between two organisms. Two organisms that interact with each other can have a <u>parasitic</u> (good, bad), <u>commensal</u> (good, neutral), or <u>mutualistic</u> (good, good) relationship.

Pathogens: <u>Anything that relies on damaging others to survive</u>

- **Primary** pathogens: will infect the host organism > 80% of the time if present (
    - e.g. Malaria
- **Opportunistic**: will infect when the host is compromised (e.g. through surgery, cold)
    - E.g. Influenza, TB
- **Properties for any pathogen:**
    - Commensal v pathogen – one is +/0, the other is +/- (parasitic)
    - Commensal -. Opportunistic – when host is compromised
    - **How does it cause disease?**
    - **Virulence:** the ability of a disease to infect/damage a host

Convergence model:

- The most modern model of host-parasite interaction now integrates:
    - Ecologic, genetic/biologic, physical environment, and social/political/economic factors
    - Original one only had covert, overt, and colonize between parasite and host.

Two worlds:

- In terms of infectious disease: we see that the Rich v Poor really create a huge stratification in terms of what disease actually kill.
    - From the 1900 -> 2000, rich got really good at stopping infectious disease, but that's not true of the infrastructure in the poorer countries

Pathogen Emergence:

- Most infectious diseases aren't new, but ar e newly discovered/ newly introduced to a new area.
    - Sometimes disease aren't recognized as an infectious disease
        - E.g. H. Pylori, Chlamydia pneumoniae
    - The pathogen was hard to identify (we couldn't culture it)
        - E.g. Legionaire's disease
    - The virulent organism is introduced to a new area!
        - Measles
- Sometimes there' new or evolved organisms, especially from animals
- The they things you ***NEED*** for this to occur though:
    - Populations need to be large enough (e.g. Measles population for 5000 years)
    - Poverty, Competition for food, Crowding, and sufficient evolution!

Zoonotic pathogens also play a huge part in this (majority of all diseases, 60% of all human, 75% of emerging) – new disease that have effectively been cultured in animals are newly introduced all the time. They go through 5 stages:

- **Not present in humans (normally)**
- **Present in humans, transiently**
- **Can go thorugh a few cycles**
- **Can go through many cycles**
- **Only in humans**

- **Biggest cause? Livestock!**

    - Burden on a billion poor livestock keepers.

- Examples of species: HIV, West nile, BSE, SARS, etc.

The Microbiome

- **A huge factor in diseases:** linked to processing xenobiotics, etc. and shown to really affect a large swath of disease e.g. obesity, autoimmune disease, kwashiorkor, etc.
- Where does the microbiome come from?
    - Birth (vaginal canal)
    - Breast feeding
    - Food
    - Env
    - Animals
- Whathas changed it in the last few decades?
    - Antibiotics
    - Smaller families
    - Cleaner homes and society
    - C-sections and formula feeding

Gender differences

- STI/UTI in female
- Autoimmune disorders 3:1 more common in female
- Females immune system typically more permissive during pregnancy
- Males tend to have higher mortality from any infectious disease

DETERMINING CAUSALITY

- **5 approaches** for providing evidence that a pathogen is a cause of a disease
    - **Koch-Henle Postulates**
    - **Evan's immunological proof** of disease causation
    - **Shepard's** proof of human teratogenicity (i.e. inheritable)
    - **Hill's criteria** for disease criteria
    - **Epidemiologic** evidence of causality

- **HK Postulates:**
  - 1 – organism always in diseased tissue
  - 2 – organism isolated in culture
  - 3 – Culture must cause disease in an animal model
  - 4 – The same organism is isolate from the animal.
- **3 situations in which HK postulates** fail:
  - The organism cannot be culture in vitro
  - There are no animal models for the organism (the disease)
  - Animal models does not reproduce the same disease that occurs in humans (HIV/ZKV both fail here)
- **Evan's proof:**
  - Antibody is absent prior to the disease/exposure to agnet
  - Antibody appears during illness
  - Presence of antibody = resistance to the disease
  - Absence = susceptibility to disease
  - Only one agent is associated unless we have cofactors
- Describe **Shepard's "proof" of human teratogenicity** of an infectious agent (only 1,3,4 essential):
  - **Proven exposure during** prenatal development (to agent)
  - **Consistent findings** by greater than 2 high quality epedimiologic studies that Relative Risk is greater than 6
  - **Careful delineation of clinical cases** (where specific people have it and others don't, I think)
  - **Rare environmental exposure associated with rare defect** (so "independent")
  - **Teratogenicity in some experimental animals** are great but not necessary
  - **Biologic Sense**
  - Proof in an experimental system that the agent acts in an unaltered state
- **Hill's Criteria: (KNOW the limitations!)**
  - Strength – How strongly can we correlate virus <-> disease?
  - Consistency – Ho consistently do you detect virus when disease occurs? An vv?
  - Specificity – How specific are the symptoms to the disease – can you rule out all others?
  - Temporality – does the symptom happen AFTER exposure – REQUIRED.
  - Biologic Plausibility – Does it make sense?
  - Gradient – Greater exposure should generally lead to more disease
  - Coherence – epidemiology coherent with lab is good but not necessary

    - Experimental evidence – previous models increase likelihood
    - Analogy – do similar things happen in other viruses/agents?
- **Epidemic Evidence** of causality:
    - **Identify an organism** to be associated with a disease in an outbreak
    - Identify the **same organism in multiple outbreaks of identical disease** at different places and times.
    - Conduct a prospective study of endemic manifestation of the same disease and show that the same organism is associated with the disease
    - Show that the risk factor for infection with the organism is the same, or related.

CLINICAL SPECTRUM

- **Name 3 examples of communicable agents that cause infectious disease**
    - (NB: This is acquired through P2P or P2Animal)
    - Ebola, Influenza, Herpes, TB, Salmonella, HIV
- **Name 3 examples of non-communicable agents that cause infectious diasease**
    - NB: Acquired through exposure to reservoirs (Non P or A)
    - Cholera, Anthrax, Clostridium Botulinum
- **Describe 3 types of asymptomatic infection**
    - Latent infection
    - Chronic infection
    - Convalescent carriage
- INFECTION VS. DISEASE
    - Infection is when you get colonized by an organism, with or without symptoms
    - Disease is when you have clinical overt symptom.
- **Components of disease spectrum**
    - Exposure
    - Incubation period
    - Asymptomatic infection
    - Symptomatic infection
    - Outcomes
        - What the primary outcome of the disease?
        - Spontaneous clearance, carriage (convalescent/chronic (1year +) Latent infection, Acquisition of immunity

    - Sequelae
        - Complications afterwards, probably death lolol.
- **Describe how the duration of incubation period affects disease outcome**
    - Long infections seem to indicate chronicity. Is this correct?
- **Name 5 factors that influence the chance of disease manifestation after exposure to an infectious agent**
    - Infectious dose/inoculum size
        - Variants of ecoli (e.g. diarrhea)
    - Vehicle of infectious agent (milk (e.g. cause it neutralizes) - water)
    - Virulence characteristic of the microbe
    - Host susceptibility (Underlying medical conditions, Medications)
    - Pre-existing host immunity/resistance (innate, previous infection, vaccination, genes)

EPIDEMIOLOGY

- **Define epidemiology as applied to infectious diseases**
    - The study of distribution and determinants of distribution of disease caused by infectious agents
- **The 7 components of EPI in ID:**
    - Disease Occurrence (localized in time and in place)
    - Reservoir of infectious agents
    - Modes of Transmission
    - Setting of disease transmission
    - Pathogen factors that influence transmission)
    - Host factors (that influence transmission)
    - Environmental factors (that influence transmission)
- **Name the three types of occurrence of infectious disease:**
    - Endemic – occurrence of disease with no apparent fluctuation wrt place and time
    - Epidemic – occurrence above what is expected from endemic levels
    - Pandemic – epidemic encompassing a large geographical area (multi country/continents)
- **Name Three major examples of reservoir and pathogens associated with those reservoirs:**
    - Human host as sole reservoir – S. Typhi, Shigella, HIV, Plasmodium Falciparum
    - Animals as reservoir: Salmonella enteritidis (poultry/egs), E. coli O157:H7, E.coli
    - Environment as reservoir: Vibrio cholerae in estuaries

- **List 10 modes of transmission of infectious disease**
    - P2P – Fecal Oral, Other-secretions oral, Perinatal
    - Foodborne
    - Waterborne
    - Airborne
    - Fomites (dirty non-living object)
    - Vector-borne (arthropod, cat?)
    - Blood/blood products
    - Organ transplants
    - Lab exposure
- **Describe 5 different settings that facilitate infectious disease transmission**
    - Community
    - Family
    - Nosocomial (Hospital)
    - Large institutions (school, day-care, chronic care facilities, military barracks)
    - Misc. (Religious gatherings, camps, food distribution systems, travel)
- **Describe 5 pathogen-related factors that affect transmission**
    - Inoculum
    - Route of infection (tells you if you'll develop symptoms/what they might be)
    - Virulence of organism
    - Defense properties of an organism (e.g. against immune system)
    - Drug resistance
- **Describe 5 host related factors**
    - Demographic: Age,gender, ethnic background
    - Immunity (innate/acquired)
    - Underlying illnesses and malnutrition etc.
    - Drug exposure (antibiotics, antacids, immunosuppresants)
    - Risky behavior (sticking needles, etc.) cultural practices (e.g. Belgians and their weird shit)
- **Describe 8 environmental factors**
    - Geography
    - Weather

- Disasters
- Industrialization
- Technology
- Population sizes/urbanization
- Socioeconomic factors. (poverty, breakdown in public health infrastructure)

MICROBIOLOGY

- **5 classes of infectious agents**
  - Bacteria
  - Viruses
  - Fungi
  - Parasites
  - Prions
- **Characteristics of infectious agents used to classify/group them**
  - Morphologic

	Bact	Viruses	Fungi	Parasites	Prions
Nucleus?	No	No	Yes	Yes	No
Cell wall	Yes	No	Yes	No	No
Plasma Membrane	Yes	No	Yes	Yes	No
Cell organelles	No	No	Yes	Yes	No

  - Growth
  - Biochemical
  - Serologic/immunologic (what do they induce)
  - Functional/physiologic characteristics
    - Antibiotic susceptibility
    - Cell culture
    - Toxigenicity assays
    - Phage typing
  - Genetic

- **5 ways in which microbes can be taxonomically classified**
    - Morph, Growth, Biochemical, Serological, Genetic.
- **Describe the key features that differentiate the two major groups of bacteria**
    - Gram pos vs gram negative. Gram negative have a double membrane, and are minimally stained due to a thin PEPTIDOGYLCAN layer. Gram positive have a large peptidoglycan layer and one membrane.
    - Other stain is the Ziehl Neelsen acid fast stain, which stains microbacteria's mycolic acid layer.
- **Name 3 ways in which bacteria exchange genetic materials, and why these processes are important for infectious disease:**
    - Conjugation, Transduction, Transformations.
    - (extra chromosomal elements nclude plasmid, bacteriophage, mitochondria, kietoplasts)
- **Name 5 characteristics of microbes that induce disease in an infected person**
    - Toxins
    - Proliferation in organ/cells by invasive pathogens
    - Overgrowth in organ
    - Host's aberrant immune response to pathogen (e.g. TB)
    - Host's immune deficiency
    - But also:
        - Cell attachment, invasion, cell death
        - Recognized virulence determinants: plasmids, converting phages, pathogenicity islands, type III secretion system
        - Mechanisms of resistance to host's antimicrobial effector molecules
        - Host subversion, molecular mimicry
        - Establishment of latency/persistence
        - Regulation of virulence genes
        - Think about all of these as a function of "they're just trying to survive"
- **Name 3 major groups of toxins produced by bacteria and the types of disease associated with them.**
    - Toxins should always be proteins, cept LPS. They have an active domain and a binding domain
    - Exotoxin – proteins secreted by bacteria, that are preformed (e.g. Staphylo toxin, toxic shock syndrome). Preformed before infection.
    - Enterotoxin – proteins secreted by bacteria after infection, not present preformed. (e.g. Choleratoxin, from E. Coli)
    - Endotoxin: A lipopolysaccharide. Can cause issues in the way of a septic shock

INNATE IMMUNITY

- **Name the two components of the human immune system:**
    - Innate
    - Acquired
        - Humoral
            - Helper B cells
            - Plasma cells
        - Cell-mediated
            - Cytotoxic T cells (CD8+ T cells) (which are the only one that can kill infected cells)
            - Helper T cells (CD4+ T cells) (which make cytokines)
                - Th1 (IFN gamm, TNF alpha)
                - Th2 (IL-4, IL-6)
                - Treg (IL-10, TGF beta)
                - Th17 (IL-17)
- **Explain the relevance of immunology to infectious disease and public health**
    - (My thought – we need to know how the body mounts its defense in order to a) diagnose what response is happening, and b) figure out how we can support it)
    - We can discover correlates of protection for the disease
    - What parts of the immune system is more important for protection
    - How much of the pathology is occurring due to the immune response
    - Are protective antigens known?
    - Can we use vaccines to help protect? Does it exist already, can a protective version be developed?
- **Describe the importance of immunity to vaccine-preventable disease**
    - Route of vaccine delivery (skin, mucosal penetration)
    - Vaccine formulation (killed, attenuated, subunit, DNA)
    - Enhancement of innate immunity by adjuvants (cytokines, chemokines, antigen presentation)
    - Blocking of receptors used by pathogens for cell entry (innate immunity cell types)
    - Inhibition of pathologic immune response (cytokines)
- **Describe disorders associated with disruption of normal immune response**

- Acquired immunodeficiencies: AIDS, DM, Chemotherapy
- Aberrant responses – Autoimmunity, rheumatic heart disease, Guillain-barre syndrome, and allergies
- Other examples of autoimmune – Multiple Sclerosis, Diabetes melitus

Innate immunity is what you're born with.

- **Key features:**
  - Responds to microbes/host cells damage by microbes
  - Has specificity, but not random
  - The first early defense
  - Prepares the adaptive immune response
  - Has no memory
  - Does not react against host
- Mechanical and physical barriers (e.g. epithelial cell barrier, mucus membrane, tears, saliva, ability to pee/cough
- Cells:
  - Phagocytes (Neutrophils i.e. the first line, /Monocytes)
  - Natural Killer cells – destroy virus-infected/tumour cells.
  - Mast cells, thought to be good against parasites, recruits basophils and Eosinophils.
  - Dendritic cells – the presenter of antigens, APC (link acquired to innate)
- Proteins etc. etc.
  - Toll-like receptors (one type of PRR) recognize Pathogen associated molecular patterns or PAMPS
  - Other pRRs (Cytosolic nucleic acid sensing PRRs)
  - Cytokines are released by activated macrophages, and affect function and behavior of other cells (TNF alpha, IL-1, IL-6, IL-8, IL-12 etc.)
  - Chemokines are signals for phagocytotic cells and lymphocytes
  - Chemokine receptors are receptors that bind to cytokines/chemokines on phagocytic cells/lymphocytes respectively
- Basic inflammatory response:
  - Bacteria trigger macrophages to release cytokines
  - Vasodilation and vascular permeability cause redness, heat, swelling
  - Inflammatory cells migrate into the tissue, releasing mediators that cause pain
- Know why need to know about innate for vaccine

Adaptive Immunity – what you acquire after you're born

- **DEFINITIONS:**

    - **Antibody/Immunoglobulin** – a protein produced by a plasma cell
    - **Antigen**: a molecule that elicts an antibody response against itself; antigen recognized by antibody to be foreign
    - **Hapten**: type of antigen that can't normally elicit an antibody response, but when complex into a larger molecule, does.
    - **Epitopes/Determinants**: parts of antigens recognized by antibodies
- **Humoral Immunity**
    - **Summary:** Antibodies are the main effector molecules. They recognize peptides/polysaccharides, lipids. They can't enter cells, so it can only recognize extracellular microbes
    - B cells -> Plasma cells in lymphoid, start making antibodies
    - Types of IGs:
        - **IgM**: Protects at early phase of infection, lyses microbes, receptor for activation of B cells
        - **IgG** protects against bacteria, viruses, enhances phagocytosis, neutralizes toxins (and crosses placental barrier, i.e. inheritance!)
        - **IgA** protects against infection on mucous membranes
        - **IgD** used to activate B cells
        - **IgE** involved in allergic responses
    - **In diagnosis, IgM = recent, IgG = long term**
    - Link to vaccine development (e.g. antibodies)
        - Level of antibody response sometimes used as a Correlate of Protection
        - Type of antibody response can predict what is actually protective
        - Most currently approved vaccine work by inducing a humoural response.
- Correlates of Protection – Anything you can measure that indicates immunity

Drug Resistant Infections, or AHHH ANTIBODIES –

- **Define antibiotics, anti-infectives, antisepctics**
    - Antibodies: substances made by **bacteria and fungi** that suppress the growth of other microorganisms or kill them
    - Antimicrobial agents – made from any source and used to treat bacterial and fungal infections
    - Anti-infectives: Antibacterial/fungal/viral/paraisitic agents used to **treat** infections
    - Antisepctics: Antiinfectives, but used to DISINFECT contaminated surfaces.
- **Name 5 major categories of antimicrobial agents:**
    - Beta Lactams

    - Aminoglycosides
    - Fluoroquinolones
    - Tetracyclines
    - Macrolides
- **Name 3 different methods for testing drug resistance in bacteria**
    - Disk diffusion test – does placing the drug into culture create a ZONE OF INHIBITION?
    - E-test – Does placing a exponentially decreasing strip of create a zone of inhibition? At which concentration of drug does it work?
    - Broth microdilution assay: at serial dilution level – what level of drug that stops or kills all bacteria. (bacteriostatic or bactericidal)
- **Name 4 mechanisms by which pathogens gain resistance to drugs:**
    - Alteration in drug target 9e..g creat a penicillin binding protein)
    - Inactivation/modification of the drug (e.g. beta-lacatamases snipping those rings)
    - Inductions of the proteins that remove the drug from the organism (efflux pumps)
    - Inactivation of the enzymes that activate the drug (indirect inhibition of drug)
- **Name 3 groups of bacterial pathogens considered by CDC to be urgent threats**
    - Clostridium Difficile
    - Carbapenem-resistant Enterobacteriaceae
    - Drug-resistant Neisseria gonorrheoeae
- **Describe why these groups are considered "urgent"**
    - They're extremely drug resistant, and thus can't actually be treated.
- **Name 5 bacterial pathogens included by the CDC to be "serious"**
    - DR-Salmonella Typhi
    - DR- non-typhoidal Salmoneall
    - DR- Shigella
    - DR Tuberculosis
    - MRSA – Methicillin resistant Staphylococcus aureus.
- **Name 3 bacterial pathogens that are most frequently associated with hospital infections; name 3 associated with community acquired infections**
    - Hospital: C-difficile, Enterococcus spp, Staphylcocus aureus (MRSA, etc.), E.coli
    - Community: UTi via Ecoli, Enterobacetriaceae – Ecoli, Vibrio Choleraea, Campylobacter

- **Name 2 major settings in which drug-resistant organisms may get selected**:
    - Hospitals (for disease), and large agricultural farms (for fattening)
- **Describe 2 ways in which clonal lineages of drug-resistant bacterial pathogens may get disseminated globally:**
    - Travel (tourism/medical tourism)
    - Global food trade
    - Companion animals (LIKE CATS)

LABORATORY DIAGNOSTIC METHOD:

- **Be familiar with the steps used to isolate a microbe from sterile and non-sterile body sources.**
    - Grab microbial population in "sterile" or non-steril niche
    - Select against unwanted microbes (if known, and non-sterile)
    - Pure culture
    - Identification!
- **Name 3 methods used to identify a microbe after it is isolated.**
    - Staining
    - Direct Fluorescent Antibody test
    - Culture
    - Molecular testing!
- **Describe 3 methods that target a host to diagnose infectious diseases.**
    - Serology (measurement of immunoglobulin/immune system)
    - T cell response
    - Imaging, like with bone scans!
- **Name 3 major microscopic staining procedures.**
    - Gram Stain (Crystal violet, counterstain with safranin. Violet for pos, Pink for neg)
        - Read: Gram status, cellshape (cocci vs bacilli), arrangement (of cocci)
    - **Acid Fast:**
        - Stains Mycolic layer, for mycobacteria, uses carbol fuschin, counterstain with methylene blue
    - **Trichrome:**
        - Detection of instestinal protozoa – stains internal structure of cysts/trophozoites, and then morphology used to identifiy
    - **Giemsa** – blood film stain for detection of parasites

- **Understand the difference between enrichment, selective, differential, and specialized medium.**
    - Enriched media: allows for the growth of most organisms, used when thought to be largely clean (CSF, blood)
    - Selective media – selects for specific organisms or groups of organisms
    - Differential – allows for the differentiation based on macroscopy activity (like MacConkey Agar for lactose processing, ecarbohydrate + pH to detect those whof eremnt carbohydrate)
    - Specialized media – some organisms need this to grow, like Legionella (Needs L-cysteine)
- **Name and describe 5 immunological methods used to detect a pathogen.**
    - IFA
    - DFA
    - ELISA
    - Latex Agglutination
- **Name 2 molecular microbiologic methods used to detect a pathogen.**
    - **DNA probes, NAATs (including PCR)**
    - **MALDI-TOF** mass spectroscopy – uses proteins to figure it out (less spectral data, wider applications

Diseases:

DIARRHEAL DISEASES:

Overview	Secretory Diarrhea (severe, loose, watery stool)	Invasive Diarrhea Acute, enteric illness -> diarrhea + fever + some evidence of enteric inflammation (pus, mucus, blood)	Persistent Diarrhea	A/E Lesion Diarrhea
Eitiology	Paradigm: *Vibrio Cholerae* Two biotypes: (Classical [susceptible to polymyxin B], El Tor (hemolytic)) Serotypes: Ogawa, Inaba, HIkojima (based on o1 antigens ABC, identification based on tests against antigens. V. Cholerae O1 toxoigenic, V Cholerae O139 cause cholerae. All others Os cause diarrhea/infection. (other examples, ETEC)	Paradigm: *Salmonella enterica/bongori* (salmonellosis, sep by rRNA) Enteritica 6 subspecies, I is most important (II-VI cold blooded) I divided further: *S typhimurium, enteritidis, Heidelberg* Other examples: *shigella, s. dystenteria, EIEC, Campylobacter, Entamoeba histolytica* *All gram negative should habve a thype 3 secretion system.*	Paradigm cause it's the only one EAggEC	Paradigm EPEC
Clinical Spectrum	**Cholera:** 1-3 days incubation Asymptomatic/mild vs Sever:	**Typhoid Fever: *S. Typhi/ Paratyphi A-C*** 1-6 week incubation.	Secretory Diarrhealike.	Prolong, loose stool, watery diarrhea, low grade fever

	7:1, El Tor, 1:1 Classical **Cholera Gravis:** Rice water stools, absent peripheral pulses, poor skin turgor, etc. Mortality 50-70% if untreated. Chronic asymp carriage rare, carriage typically 2 weeks. **General Secretory Diarrhea** Very watery stool, dehydration, low grade fever Not as bad as Cholera due to reversabel rxn.	Bloodstream infection/diarrhea not prominent. Complicated into intestinal hemorrhage, hepatitis plus other infect. Chronic carriage (1-3%) **Non-Typhoidal salmonellosis/enterocolitis** Asymptomatic infection most of time. Incubation for 12-72 hrs, dep. Infect mode. Nausea, vomiting, chills, then colon-releated pain, diarrhea, fever, sometimes bloody stool, 1-5 days. Convalescent carriages: 5 weeks median Chronic carriage < 1%.		
Epidemiology:	**Reservoir:** Brackish water, esturiary, shellfish, water plants, algae **Transmission:** Fecal Oral, Water, Foodborne (seafood, lettuce, crops irrigated with sewage, etc.) **Occurrence:** VC – 1E6,7	**Reservoir:** P (S typhi/ SPT A), or P/A (most others) Enteriditis: poultry Typhimurium: cattle, poultry Urbana: turtles **Transmission:** Main sources – contam water/food. Huge issue: centralized food production.	Resevoir unknown High inoculum (1e9,10)	**Reservoir:** Human and possibly animals **Transmission** P2P Occ: 1E7,8

	ETEC 1E5,6 **Risk factors**: Enviroment: residence in endemic areas, war/disaster torn environment. Host: Low gastric acidity, blood type O, bottle feeding Strain factor: El Tor is largely asymptomatic, less immunogenic, and duration is longer surviving.	Non-typhoidal – Fecal oral, foodborne most prominent **Occurrence:** Sal – 1E3-9, sever infections typically <5 or >65 yo. **Seasonal variation:** Summer highs		
Pathogenesis	Initially adheres to the brush border, attaches to M cells. Toxin coregulated pilus/other pili/fimbrae connect. Release cholera toxin, binds to GM1, subunit causes ADP ribosylation of a GTP binding protein, activates adenylate cyclase, pumps cAMP levels up, causes chlorde secretion into the lumen and loss of electrolytes.	**Salmonella**: Enter through M cells in Peyer's patch, taken up by macrophages, survive/replicate within it, (inhibit phagosome-lysosome fusion, inhibit phagosome acidification, resist ROS, resist lysosomal enzymes, escape the phagosome) burst out and go to the blood stream/lymph systems! Destroy som cell! Virulence factors: Type 3 secretion apparatus – Comprised of proteins that form "needle complex" and "effector" molecules, with genes	Toxins, similar to ST enterotoxin.	Erasement of Microvilli via BFP, espA/b/C, then TIR + intimin. Leads to malabsorption.

	Virulence factor: Pathogenicity is phage encoded (both CTX, and TCP)	located in Sp 1 (of 5 pathogenicity islands in typhimurium). Lots of virulence plasmids.		
Diagnosis	Testing for vibriocidal antibody	Salmonella reporting: The population becomes ill. The person seeks care and the specimen is obtained. This is sent to the laboratory, which confirms the case and reports to the CDC Enteric Fever: Bone marrow culture, serologic tests, PCR.		
Treatment	Rehydration with electrolytes! Antibiotics not recommended, as typically its transient (4-6 days)	Antibiotics Since intra-cellular parasite, need cell mediated immunity to remove pathogen.	Improve nutriotion, possibly antibiotics.	Rehydration, antibiotics
Prevention	Vaccine: See later section. Immunity: Classical helped a lot, El Tor not at all. In studies – similar but El Tor was 90% okay for disease and 70% okay for infection.	Typhoid vaccine: Whole cell, inactivated parental vaccine. (2-3 every 5 years) Whole cell attenuated oral Ty21a (3-4 dose, 4 years) Subunti, Vi antigen vaccine – 1 dose, booster 2 yars. Subunit, Vi-rEPA vaccine ViRepa most effect, then liquid Ty21, then Viantigen.		

	IgA produced after the initial adherence to M cells. Corellates of protection: Vibriocidal antibody Antitoxic antibody.	2014 study – no real CoP.		

Cholera Vaccine:

- What types of vaccines are there?
    - Whole cell, killed – parenteral/oral
    - Whole cell, attenuated – oral
    - B-subunit (Thing that binds to GM1) + whole cell
- Licensed oral vaccine:
    - Dukoral – B subunit + heat/formalin killed V. cholerae
    - Sanchol – killed V. cholerae O1 and O139

- Why is the vehicle about the antacids, group!.
- A bit about genetics of cholrea – phage-encoded – virus injected.

Diarrhegenic Ecoli Common themes:

- **COLONIZATION FACTORS** dictate who gets infected
- Virulence factors encoded by DNA elements **(PLASMIDS, PHAGES)**
- Pathogenicity isalnds facilitate bacteria-cell interaction
- **Ecoli host** that gains a new converting phage -> new disease!

	EPEC	ETEC	EIEC	EHEC
Summary	Prolonged loose stool and watery diarrhea, low grade fever, sometimes persistent Major cause of diarrhea in urban centres in dev-ig countries, high mortality Freq drug resistant Reservoir is human + possib animals Transmission is P2P. Inoculum 10^7-8	E coli that have one or two enterotpoxins, ST>/LT Secretory diarrhea -- watery diarrhea, low-grade fever Worldwide; most common case of traveller's diarrhea and has high morbidity (due to higher prevalence Reservoir - animals (possibly), environment (possibly), humans Trans - p2p, water, foods Inoculum 10^8	Invasive (inflammatory) diarrhea Worldwide Reservoir: human Infectious inoculum: 10-100	Causes *hemorrhagic colitus*, *hemolytic uremic syndrome* (5-6%, children), and *thrombotic thrombocytopenic purpura* (adults) Mortality in small children, elderly high Found in largely industrialized countries (esp. with centralized cattle industry) **Reservoir**: cattle **Transmission**: food, esp cattle associated (beef/milk/water/produce contaminanted), P2P has been observed.
Pathogenesis	**Initial adherence:** Bundle-forming pili, encoded by plasmid, mediates attatchment **Intimin indpeendent signalling** EspA/B/D are secreted, to host cells, causing: -Cytoskeletal rearrangement (chops up actin and moves them etc. towards the bacteria)	**Colonization factor antigens** (what help them adhere to small bowl enterocyte) are fimbrial structures (encoded by plasmid) - tell sus what they can actually infect The same plasmid encode the **two enterotoxins**: <u>LT - Heat Labile</u>	Invasive mediated by a 140-Mda plasmid containing genes identical to shigella for cell invasion From ref - penetrates epethilial cells, lyses the endocytic vacuole (to get in), multiplies within the cell, moves through the cytoplasm, goes to adjacent cells!	**Shares virulence factors with EPEC** (intimin, tIR, secretion apparatus protines, but no BFP) Ecretes Shigatoxins, which inhibits protein syntehsis after binding to receptor Gb3, causes cell death. - STI (stable toxin I) antigenically identical to Shigatoxin

	- Pedestal formation (outter membrane etc. moves towards the bacteria.. I think) -Microvilli effacement - microvilli erased, is this part of the acting choppin? **Intimin dependent signalling** Translocation of the TIR (translocated intimin receptor) allows for the intimin, an outer membrane protein on the EPEC, to be attached to the pedestal, completing the attatchment	- Resembles Cholera enterotoxin (CT, activates adenylate cyclase - Raises cAMP, which phosphorylates a bunch of chloride channels, stimulas tonnes of cl- secretion, increase ion apparently draws more water, and causes wattery diarrhea. *ST - Heat Stable - (Sta or STI, STb or STII)* STA activates guanylate cyclase, which causes elevation in cyclic gmp, leading to the same effect. effect is reverable, may also activate protein kinase C STB (from ref appears to destroy villi epithelial cells. Stimulates bicarbonate secretion. + calcium.	In severe infection, inflammatory rection = ulcer! Also release toxins	- STII epidemiologically associated with HUS - Can destroy lining, cause watery diarrhea - So both destruction of villi and also shigatoxins
Detection	Serologic - serotype association with pathogenic group: Various Bioassays: Gene probes, PCR for various unique fragments.			
Treatment	**Rehydration**	**Rehydration+ antibio**	Antibio	**Supportive care, Never antibiotics (cause that rupturs cells and release MORE TOXINS)**

AFLATOXINS AND OTHER MYCOTOXINS:

- **A. What are mycotoxins and mycotoxicosis?**
  - **a.** Mycotoxin - a lowweight secondary metabolite of filmaentous fungi that cause disease/death in humans and other mammals/organisms
  - **b.** Mycotoxicosis: the diseases that are caused by mycotoxins (different from mycoses, which are the disease caused directly by fungi)
- **B. Name the mycotoxins that cause human disease and the associated diseases**
  - **a.** Aflatoxin:
    - **i.** Acute exposure causes:
      1. Toxicity uncommon in humans
      2. Liver damage (fatty liver)
      3. Kidney /heart involvvement (they're also damaged possibly
      4. Cerebral edema, convulsions, coma
      5. Death
         - **a.** 10-20mg for aflatoxin
    - **ii.** Chronic exposure
      1. Cancer
         - **a.** Primary hepatocelular carcinoma (HBV major risk factor)
         - **b.** Pulmonary carcinogen in animal tests
      2. Immuno suppresion
      3. Child growth impariment
  - **b.** Citrinin
    - **i.** Causes kidney damage (as a nephrotoxin
  - **c.** Ergot Alkaloids
    - **i.** Causes convulsion, gangrene, and st. anthony's fire (ergotism)
  - **d.** Fumonisns
    - **i.** Causes diarrhea, possibly esophogeal cancer, and defect
  - **e.** Deoxynivalenol
    - **i.** Immunoxtoxic causing gastroenteritis
  - **f.** Ochratoxin
    - **i.** Another nephrotoxin
- **C. Describe the factors that contribute to exposure to mycotoxin**

a. Pre harvest conditions such as High temperatures, prolongued drout conditions, and high insect conditions
b. Post harvest conditions (warm temperatures, high humidity)

HELIOBACTER

- **Describe one unique microbiologic feature of H. Pylori that enables it to colonize the stomach**
  - H Pylori produces urease, which hydrolizes urea to yield ammonia, providing a neutral area (after reacting with the acidic stomach acid) for it to survive.
  - Chemotaxis to get away from high acidity.
- **Name the 4 clinical syndromes associated with H. Pylori**
  - Gastritis
  - Peptic ulcer disease
  - Gastric adenocarcinoma
  - Gastric lymphoma
- **Name the major recognized virulence factors of H. pylori**
  - **oipA, sabA, sabB, babA, babC, and hopZ, all help protect H pylori**
  - It coats itself with host proteins
  - Has LPS protection to hide itself too!
  - CagA induces expression of SMO, induceses peroxide protduction which is BAD
    - Also induces epithelial cell proliferation
    - Also alters p53 expression (tumour suppressor protein)
    - Also induces IL-8, which has been implicated in colorectal cancer
    - All help cause cancer oh no
  - VacA
    - Alters endosomal maturation, leads to epithelial cell vacuolisal
  - DupA
    - Associated with risk of duodenal ulcer!
    - Induces IL-8 from the antral region
  - IceA
    - Associated with peptic ulcer disease
  - Outer inflammatory protein (oipA)(of HopH)
    - Induces mucosal IL-8

Other things:

- **Reservoir:** Humans, in stomach, early infection, very persistent
- **Transmission:** P2P – cavities, vomit, possibly water? Risk factor with SIBLINGS.

- **Prevention:** Increase socioeconomic status, hygiene. Vaccine in dev but CoP not definitive.
- **Peptic Ulcer Disease:**
  - *H. pylori* colonizes the antral region of the stomach
  - Gastrin is stimulated
  - Gastrin causes excessive acid secretion
  - Increased acid secretion leads to further cell damage, increased colonization by *H. pylori*, and inflammation---ulcer
  - Damaged mucosa may be recolonized with enteric microbiota→disease progression
- **Diagnosis**: gastric biopsy, serology IgG, Urea breath test (exhaled Co2 from C13 labelled Urea), stool tests.

HEPATITIS:

	A	B	C	D	E
Genetic material	RNA virus	DNA virus	RNA virus	RNA virus	RNA virus
Epidemiology	Declining due to vaccine	Declining due to vaccine	Increasing in USA	Needs Hep. B	Associated with sanitation. Zoonotic and human reservoirs
Transmission	Fecal-oral	Blood-borne Vertical transmission	Blood Vertical transmission	Blood borne	Fecal-oral
Prevention	Hygiene	Vaccine	Harm reduction	No transfusion with Hep B positive blood	
Treatment	Supportive	Antivirals	Antivirals	Treat Hep B	Supportive
Vaccine	Yes	Yes	No	See Hep B	
Chronic infection, HCC, Cirrhosis	No	Yes	Yes	Yes with Hep B	No

Hepatitis A:

- **Why genotype this virus?** It has only one serotype, but multiple genotypes. We can use this genotype to trace the route of outbreaks (e.g. frozen berries, etc.)
- **Who is at risk for becoming infected:** Basically, poor people/countries and people without good sanitation, as well as injection drug users, peole in crowded areas, etc.
- **How has the incidence of this disease in the US changed in the last 5 years:** Increase recently – Due to outbreaks in places such as homeless camps with contaminated needles.
- **How is this virus transmitted:** Largely through fecal oral route. You shed a lot in your stool when you're viremic, though your blood typically doesn't keep it. Also, contaminated outbreaks, and common source outbreaks (frozen berries)
- **How is it different from HBV, HCV?** Not chronic, unlikely to generate hepatocellular carcinoma or cirrhosis, no extrahepatic manifestation, present in feces.
- **How is this disease diagnosed? Measurement of IgM and IgG**. IgM indicates acuteness, IgG indicates a past infection/immunity. Also, Liver function tests, Culture, and PcR.
- **How can infection be prevented?** With proper hygiene, and harm reduction, ideally.

OTHER FRAMEWORKT HINGS:

- **Colonization/Pathogenesis:** Hep A is ingested, replicates a little in the GI tract (though we don't know what cell allows for it). It then hits the liver,w here it really replicates in hepatocytes. The inflammation then occurs, damaging the liver. It is then transported to intestines and is shed in feces.
- **Epidemiology -** Incubation is 15-50 days, total (mean 28-30 days)
- **Clinical Symptoms -** Largely not a problem n children, only few deveop icteric or anicteric.
- **Treatmetn – Supportive, no need for beadrest**
- **Prevention**: Defnitely, hygiene! We can use the genotyping to figure out the weak links, but hygiene + sanitation. You can use the vaccine, both before and right after infection, as well as gammaglobulins (concentrated serum from various popn).

Hepatitis B:

- **How does this virus differ structurally from the other hepatic viruses?**
    - Firstly, has a core + surface antibodies (like C), and b) it's DNA instead of RNA
- **Who is at risk for infection?** Sexual/Household contact, people infected with HIV, people who do injections, and MSM, and people who are form high endemicity levels.

- **How is the epidemiology changing in the US?** Occurrence is largely going down due to the vaccine, but pockets of Hep Boccur due to injection/drug use, as well as bad hospital sharing. Finally perinatal is still a thing, but not as bad anymore.
- **How does our immune reponse to infection determine the clinical course and prognosis?** The prognosis is largely dependent on the Cell Mediated immunity, which can recognize and destroy infected cells/downregulate viral replication (see video). However, it also contributes to long term infection, inflammation, and eventually cirrhosis.
- **What are the complications of chronic infection?** Cirrhosis and Cancer, the latter due to inflammation, the former due to viral DNA injection and time.
- **How do we diagnose acute vs Chronic infection?** We can use (e.g. HBsAb) to check for infection, and then a check on HBsAg to check for presence of virus. We can also test if a person is infectious by testing HBeAG as well as DNA directly.
- **How does the life cycle of the virus inform therapy?** Therapy typically stops more replication, but we can't cure.
- **How can we prevent infection?** Avoid unprotected sex, donated blood, if pregnant, get vaccine, Don't' share toothbrushes,razors, blades. We also need to screen way better for everything (blood pools, donation of sperm, etc.). **Finally for those who are infected, vaccine + immunoglobulin for passive and active immunization can stop it from progressing.**

Hep C:

- **How large of a problrm is HCV infection?** Very big now – its chronicity has made it overatke both A and B in the US. It's also distributed world wide relatively evenly.
- **Who is at risk?** Transmission through mother, those who receive blood transfusions, prisoners, health care workers. Transmits heavily towards women. HIV coinfection, and finally, hosptial out breaks! (For risk for accelerated fibrosis – fibrosis itself, older age, organ transplant, being male, alcohol, fatty liver, obesity).
- **How does this virus differe structurally from HBV?** RNA vs DNA
- **How does HCV's replicative cycle inform our treatment?** Each group - Protease inhibitors will break down the polypeptide protein, RNA polymerase inhibitors, and the NSSA inhibitor which break down the replication complex from the polyprotein, preventing it from replicating.
- **What is the prognosis after acute infection? 0-** 80 become chronic, less than 2% overall celear every year. It can tehn proceed to a lot of various extrahepatic manifestations (like arthritis, fatigue, and non-hodgkin lymphoma). Lots of cancer chances too.
    - You can look for Igg serologic tests, and RNA.
- **How can infection be prevented?**
    - Screen baby boomers/donors
    - Anybody who has a transfusion

    - Those who have STD likelihood
    - Drug use
    - Then pass on info to all people who might be affected!
    - NO VACCINE THOUGh since we have no CoP

Hepatitis D:

- **Who gest HDV infections?**
    - People with HBV infection
- **How is it unique among the hepatitis viruses**
    - HDV lives in HBV – parasite of a parasite. Specifically, it picks up the HBV antigens and creates itself.
- **How does it differ clinically from other viral hepatitis**
    - It's just a booster for HBV – makes B more likely to be chronic, and makes acute worsel.
- **How can it be prevented**
    - AFAWK, just prevent HBV.
- DIAGNOSIS: HDV RNA, HDag for acute, and HDV total/IgM, liver HDAg for chronic/acute super.
-

Hep E:

- **Who is at risk for this infection?**
    - Anybody who's at risk for A – Through Genotypes 1 and 2
- **How is the epidemiologhy similar to A?**
    - Genotype 1-2 is waterborne + fecal oral, Genotype 3-4 is foodborne. It's also typically not chronic. Reservoir is human (1/2), and animal (3/4).
- **What is the prognosis after infection?**
    - Typcially you're fine, develop at most mild symptoms, unless you're a pregnant woman in the 3rd trimester, for which you have much higher acute cases and mortality in general
- **How is infection diagnosed?**
    - You can use both IgM and Igg in a similar manner.
- **How can infection be prevented?**
    - Sanitation, cooking meat (for 3-4), screening, and china has a vaccine (that we don't' have yet)

From disease:

- A lot of enteric ones are gram-negative.

PH260A Midterm 2 Review

Viral Enteric Diseases

Overall:

- In developed countries viruses are the **single most important** etiologic agent of acute gastroenteritis that require hospitalization of children
    - 210,000 children per year hospitalized per year
    - Reduced by development of rotavirus
- 30-40% of US cases due to viral causes.
    - Most due to norovirus, (21 mill)
- Worse in developing countries, 330 000 deaths in children < 5, 30 mil severe cases.

Common examples:

- **Rotavirus**
- **Norovirus**
- Saporvirus
- Astrovirus
- Adenovirus
- Coronavirus – in very young children
- Influenza A – in very young children

Oral Rehydration Treatment:

- The cause of death is typically due to dehydration and malnutrition. Thus you need to rehydrate with saline+glucose
- Saline isnt' naturally absorbed in diseased state, and thus water isn't absorbed either
- Glucose in 1:1 ratio with NA+ gets cotransported, along with water.
    - Other examples – amino acids, dipeptides and tripeptides
- The discovery of ORT in 1968 dropped childhood deaths from diarrhea from 5 mill to 400k-660k. Uptake has been slow, 45% globally, US resisted until 1992.

Summary Chart for Rota and Noro

	Norovirus	Rotavirus
Incubation period	1 to 2 days	1 to 3 days
Duration	1 to 2 days	3 to 8 days
Age group	3 years to adults	0.5 to 3 years
Pathology	Blunted villi Lymphocytic infiltration	Blunted villi Lymphocytic infiltration

Rotavirus

- Etiology
  - Family: Reoviridae (respiratory enteric orphan), genus: rotavirus (comes from WHEELS)
  - Two main identifying proteins: VP4 and VP7
    - VP7 -> G-genotype (27 strains. 12 human) – forms capsule
    - VP4 -> P-genotype (35 strains, 12 human) – form the spokes
  - G1-4 and G9 predominate strains (90%), G1 = 75%
- Epidemiology:
  - Occurrence: localized largely in sub-Saharan Africa, Asia (india+laos+Bangladesh really bad)
    - Children < 5yo at risk.
    - It was a lot worse in the US before the introduction of the vaccine in 2006. Major declines are observed, in all age groups (herd immunity)
  - Reservoir
    - Group A – humans and animals, typically within same species, though interspecies has happened., e.g. canine-> human, Italy 1997.
  - Transmission:
    - F-O: 4 hours on hands, (Nosocomial, Nursing homes, Day-care centers)
    - Fomites: resistant to hard-surface disinfectants
    - Waterborne: Can survives for weeks in waters.
    - Food
  - Temporal Patterns: Typically winter-spring
  - Communicability:
    - Incubation – 1-3 days
    - Contagion – (-2)-10 days from symptoms. Immunodificiency -> >30 days.
      - Peaks at beginning of illness (10^{11}) – 10 particles can infect!
    - Neonates excrete asymptomatically, thought to be due to host factors, passive immunity, transplacental antibodies.
- Pathogenesis
  - Rotaviruses infect through trypsin digestion in small bowel (jejunum).
  - Infect the villous epithelium – Thought to be due to enterocyte destruction and malabsorption. Inflames the villi and blunt it, and eventually recover
  - After infection, they release both as free viruses and in vesicles, the latter of which has a much higher chance of infection.
  - Immunity: Most children have antibody by age 2. Targeted towards VP3 and VP7. Also given with breastfeeding.
- Clinical
  - Classic Triad - Vomiting, Fever, Profuse diarrhea
  - Dehydration (80% for a rotavirus)
  - Prognosis typically good in developed countries. NG in underdeveloped countries
  - Viremia not expected, but happens in immunocompromised.
- Diagnosis

    - Enzyme immunoassays (ELIZA, etc)
    - Latex agglutination is the most common.
- Treatment
    - ORT and IV is the most important. Immunoglobulin has been attempted but no real studies actually done
- Prevention:
    - Drink Mlik! – Human and Cow milk have IgG
    - Vaccine development has been good! (Can't just solve hygiene like bacteria)
        - Uptake has slowed due to supply constraints, high costs, and logistics. (cold storage hard, short window for vaccination, cost).
        - Rotateq, Rotashield, Rotarix.

Norovirus

- Etiology
    - Family Calciviridae, genus: Norovirus
    - VP1 protein P domain is responsible for host cell attachment and antigenicity
    - Largely GII.4 genotype. 70—80% caused by them. Variants of GP11.4 appear every 2-5years.
- Epidemiology
    - Occurence
        - 21 mil per year in US – 50% of outbreaks, 26% of ER diarrhea
        - 1/5 of all cases worldwide of acute gastroenteritis.
        - Developing countries – causes 200k deaths per year in children < 5.
        - Breakouts – spread from direct hand and ¾ outbreaks in LTC facilities.
        - We track using NoroSTAT
    - Transmission:
        - Low infectious dose + lots of viruses in each gram (few billion per gram)
        - Environmentally stable
        - Spread through:
            - There are direct contact between hosts via F.O, Contaminated foods or water (gremlins, raspberries, raw oyster). Fomites, Aerosolized particles!
            - Rapidly evolve
    - Temporal pattern, most frequent in winter.
    - Communicability: 10-51 hours, shed viruses 21 days.
    - Outbreak locations:
        - Nosocomial, LTC
        - Operation Desert Storm
        - Cruiseships!
            - Packaged Meat.
- Pathogenesis:
    - It's not very clear – it's a small bowel disease like Rotavirus
        - ABO and Lewis antigens allow for viruse binding, and seems to determine who gets infected.
    - Immunity also not clear – IgA gives some short-term protection.

- Clinical:
    - Mild-moderate bvomiting
    - Possible watery diarrhea
    - Shorter duration and No fever.
    - 10-51 hours, 2 days illness, 21 days total contagion
- Diagnosis:
    - Kaplan et al. diagnosis criteria (vomiting in 50% patients, incubation 24-48 hours, illness 12-60 hours) identifies outbreaks
    - Reverse transcriptase PCR
    - Enzyme-linked immunosorbent assay test.
- Treatment:
    - Supporrtive ORT or IV + antimotility/antisecretory agents for diarrhea prevention
- Prevention:
    - Not great but:
        - Food handler restrictions
        - Food and water precautions
        - P2P and environmental control
    - Vaccine development hampered by:
        - Lack of model shystems
        - Few human studies
        - Antigentic variation
        - Unknown duration of protective immunity
        - Unoknown effects of pre-exposure history
        - Antigenic variation among genotypes and genotypes.

Protozoal Enteric Infections

- The first animals – hunters and grazers of the microbial world.
- Wildly important for microbial flora + etc. Only a few are human pathogens
- Somwehre between 5-500 um in diameter.
- Important Examples:
- Ciliates
    - *Balantidium coli*
- Flagellates:
    - *Giardia*
    - *Trypanosoma*
    - *Trichomonas*
    - *Leishmania*
- Amoeba (belong to a larger group called Sarcodina):
    - *Entamoeba histolytica*
    - *Naegleria*
    - *Acanthamoeba*
- Sporozoa (motility is absent except male gametes):
    - *Plasmodium*

- *Toxoplasma*
- *Babesia*
- *Cryptosporidium*
- *Cyclospora*
- *Isosopria*

Giardia

- **Understand the barriers to clarifying the epidemiology of giardiasis.**
  - There's a lot of cross-species transmission, and host specificity. Moreover, most Giardia species are morphologically indistinguishable
- **Know how important giardiasis is in causing human disease.**
  - **Most common**
- **Know the typical methods of transmission of this protozoan.**
- **Be able to discuss the means of transmission of *G. intestinalis*.**
- **Eitiology**
  - First described in 1681, named in 1869, cultured in 1970s
  - **Giardia intestinalis/lamblia/duodenalis**
    - The most common protozoan enteropathogen
    - Two forms:
      - Trophozoite – 4 pairs of flagella and ventral sucking disk.
      - Cyst – Under intestinal influences, trophozoites encyst. Forming a chitin wall against environmental factors. (except drying/heating) At maturation, division can occur into two separate trophozoites.
  - Other Giardias (agilis ardeae, microti, muris, and psittaci) exist but less important.
  - **G. intestinalis** can be subdivided into genetic assemblages A-G, and further into subtypes. Each can infect a set of species,a nd some more common.

Molecular Characterization	
Assemblages	**Some Species Commonly Infected**
A-I	Humans and animals (cats, dogs, livestock, deer, muskrats, beavers, voles, guinea pigs, ferrets)
A-II	Humans (more common than A-I)
A-III and A-IV	Exclusively animals
B	Humans and animals (livestock, chinchillas, beavers, marmosets, rodents)
C and D	Dogs, coyotes
E	Alpacas, cattle, goats, pigs, sheep
F	Cats

  - **Human ones: A-I, AII, B.**
  - Outbreak source identification is nigh impossible due to the
    - Cross-species transmission, different species are often morphologically indistinguishable.
    - Source of cyst is often guesswork and circumstantial evidence
    - Possible solution: monoclonal antibodies!

- Epidemiology
    - One of the 10 most frequent infectious diseases (1.2 mil pa)
    - US: Most common waterborne outbreak cause. 20k cases reported per year
        - Commonly in children, esp <5 years old. Big issue with daycares where many children are together (52% asympt in Tuscon in daycares had Giardia vs 5% of those not)
        - Prevalence largely in the Midwest and Northeast coast
    - Reservoir: Many animals, including humans
    - Transmission: waterborne, facilitated by bad sewage/treatment systems
        - Zoonotic – anthropozoonotic cycles possible near strays/hoofed animals
        - P2P also possible.
    - Temporal Pattern: Summer!
    - Communicability: Incubation 3-25 days (median 7-10 days). Often insidious onset – difficult to detect common source outbreak.
- Pathogenesis:
    - Cysts are ingested from food/water/ p2p.
    - Excysts in small intestine
        - Attatches to intestinal epithelium using ventral disc
    - Trophozites divide by binary fission
    - Encysts, spreads.
    - Causes disease by:
        - Disruption of intestinal structure (villus atrophy
        - Intestinal dysphunction
        - Mucosal Injury from attatchment, proteases, lectin, or immune response
    - Virulence factors:
        - Attatchment via adhesive disc + lectins
        - Circumvention of natural host defense: Flagellar motility + VSPs
        - Antigenic variation prevents clearance (VSP)
        - Downregulates nitric oxide
        - Encysting.
- Clinical:
    - Incubation symptoms duration all vary greatly. 41 days for 86%, but some patients infected despite chemotherapy (possibly due to resistance)
    - Adults often asymptomatic (60%). Very common in very young and children.
    - Symptoms:
        - Watery diarrhea (no fever/blood/pus)
        - Abdominal cramping
        - Bloating, weight loss
        - Some develop persistent giardiasis, not clear – children/low immunoglobulin levels
        - Early life giardiasis is a weak riskf actor for stunting.
- Diagnosis
    - Stool analysis on 3 separate days (due to intermittent shedding)
        - Light microscopy/ Immunofluroescent

    - Small bowel analysis: biopsy/Aspirate
    - Antigen detection method
    - Diagnosis – Try multiple stool tests. Else try empiric treatment or endoscopy/biopsy. If any do positive go for treatment.
- Treatment:
    - Nitroimidazoles! (tinidazole or Metronidazole). Various other drugs possible.
- Prevention:
    - Unlikely to be eliminated due to reservoir
    - Hygiene, Food water precautions
    - Fecal exposure during sex
    - Vit A
    - Brestfeeding

Cryptosporidiosis

- Know why it is often difficult to diagnose this organism.
    - Rarely reported, rearely tested, easily missed.
- Understand why disease from this organism is particularly severe in compromised hosts. – Just not htat it is.
- Know about the outbreak in Milwaukee.
    - 1993, 400k cases, 4k hospitalizations, possible infection of lake Michigan with cattle poop
- Know why we should pasteurize milk.
    - It's a possible source! Stupid cattle
- Know who is at increased risk for infection.
    - Swimmers, Children, People who work with children/infected people
- Understand methods of prevention.
    - Water Filters, Exclusion of diarrheic children from childcare settings, don't swim while having diarrhea.
- Etiology:
    - Coccidian, Intracellular protozoan. Often *C. parvum, C. hominis* for disease (zoonotic and human specific respectively).
    - 20 species known.
- Epidemiology:
    - Occurrence: Worldwide – cimportant cause of childhood diarrhea, not the most common, but prevalent.
        - 1-3% prevalence in children with diarrhea in industrialized countries
        - 4-!7% " " in developing countries
        - Rarely reported bfore 1980.
        - Likely in Children 1-9, Adults 25-29
        - 748,000 cases pa, 2% reported
    - Temporal pattern: Late Summer
    - Risk Factors:
        - Children in daycare centers, child care workers, Parents of infected children
        - International travelers

        - Those who drink unfiltered, untreated water (swimmers, wells, backpackers),
        - Cattle farmers
        - Consuming unpasteurized milk
    - Notable outbreak in Milwalkee in 1993
        - Widespread absenteeism in hospital employees, teachers, students (diarrhea)
        - Water plant noticed "increased turbidity" Mar 21-Apr 5th
        - 2 labs identified Cryptosporidium on April 7th,
        - Advisory to boil water at 7th, closed southern plnt 9th
        - 400k ill, 4k hospitalized
        - Thought to be due to cattlefeces contamination of Lake Michigan, though plant met standards for cleanliness
    - Reservoirs:
        - Cattle, Humans, some others (chicken salad?)
    - Transmission
        - Mostly waterborne (drinking/recreational water which is contaminated
        - Sometimes foodborne as a vehicle (e.g. any raw fruit, chicken salad)
        - Touching mouth/eating contaminated food.
    - Temporal Pattern:
        - Summer and early fall
    - Communicability:
        - Incubation 5-28 days, 7-10 days to symptoms. Immediately infectious
        - Shedding 1-2 months
        - Highly infectious 10-1k oocysts needed
        - Can survive environmental pressures really well
    - Pathogenesis:
        - Oocyst ingested
        - Excyst in small intestine
        - Sporozoites released and penetrate intestinal epithelial cells.
        - Go through asexual and sexual reproduction within the cell (forming Type1 meronts/ Type II meronts respectively)
        - Sexual reproduction leads to zygote->oocysts
            - Thin walled for autoinfection, and thick walled for excretion
        - Causes malabsorption through attachment and effacement of microvilli, also leads to breakdown in typical enterocyte development during migration up villus
            - This immaturity thought to lead to failure of digestion/absorption
        - Also causes inflammatory reactions and stimulates anti-apoptotic
    - Clinical:
        - Incubation 2-10 days
        - Infection may be asymptomatic
        - Diarrhea common
            - Much more severe in immunocompromised

            - Why? Severe disease in malnourished children
            - Associated with acute malnutrition and growth stunting
            - Chronic diarrhea for HIV patients
        - 1-2 weeks in most.
    - Extraintestinal involvement happens – biliary tract + respiratory
- Diagnosis:
    - Acid Fast stain of the stool looking for oocyst
    - Cryptosporidum antigen detection (EIA)
    - PCR
    - Small bowel biopsy.
- Treatment
    - Nitazoxanide (for all!)
    - HAART for patients with Aids.
        - Suppresses their rampant immune system – helps them with fighting off disease.
- Prevention
    - Disinfectants typically don't work
    - Water filter, with < 1 micron
    - Immunocompromised people should abvoid close contact with known infections, animal feeces, or fully boild water.
    - Exclusion of diarrheic children from childcare settings
    - Recreational waters need to be properly kept clean via patron and operator diligence

Cyclosporadiasis

- Know the lifecycle of this organism and how this influences the epidemiology of disease. – The fact that it has to mature outside makes it less local and more likely to be hidden through foodborne distribution
- Understand why this organism causes foodborne outbreaks.
    - It has to mature outside the body at 22-32 degrees, so it can contaminate water/produce
- Know how to prevent outbreaks from this protozoan.
    - Food/water precautions, smart diagnosis for faster pinpointing of outbreaks (tis hard.

- Etiology:
    - Unicellualr parasite
    - Species designation – *Cyclospora cayetanensis* all human cases.
- Epidemiology
    - Largely tropical/subtropical. Many outbreaks (foodborne) in us/Canada
    - 2018 outbreak due to Salads:
        - Mcdonalds salds in Kentucky/Illinois – apparently all due to Fresh Salad processor in Streamwood. 511 cases from May 20 to Sept 11
    - Resevoir: only humans
    - Transmission:
        - Indirect fecal oral

        - Unlikely to be direct P2P, as they require some time externally to sporulate and actually become infectious
        - Virulence factors: small size, chlorine resistant, low infective dose, spreadable in environment
    - Risk Factor: All ages at risk, Travelling are increased risk, but infection is acquirable worldwide.
    - Temporal : in US, most of the cases occur during spring/summer
    - Communicability: The incubation is ~7 days, inoculum thought to be small.
- Pathogenesis
    - Freshly passed in stools, not infective
    - After a few days to week at 22-32°C, sporulates into two sporocyst each containing two sporozoites.
    - These sporulated oocysts are then transferred via produce/water
    - Ingested, the sporozoites excyst in the gastrointestines. They invade the small intestines, go through asexual/sexual multiplication to create oocytsts.
- Clinical:
    - Incubation ~ 1 week
    - Causes watery diarrhea + frequent stools
    - Loss of appetite, etc.
    - If untreated, few days to a month or longer
    - Some asymptomatic
    - Reinfections possible.
- Diagnosis
    - Stool examination over 3 days,
        - Wet mount, modified acid fast, UV microscopy
        - 7-10 microns.
    - Not commonly tested for
- Treatment
    - Trimethoprim/sulfamethoxazole shownt o be effective
- Prevention
    - Water precautions
    - Food precautions
    - In order to stop an outbreak, you need to notify producers that they're infectious
        - However, due to the waxing and waning of Cyclospora, plus concealed food vehicles makes it difficult to pinpoint without a common meal. (See the major outbreak from May to Sept 2018.

Amebiasis

- Know the difference between pathogenic and non-pathogenic species of *Entamoeba*.
- Understand how the epidemiology differs in the developed versus the under-developed parts of our world.
- Correlate the life-cycle of *E. histolytica* with the pathogenesis of disease and clinical spectrum.
- Know the important methods of preventing disease.

- Etiology:
    - Order Amoebida, Genus Entamoeba
    - E. Histolytica most common for amebiasis
    - E. Coli (gosh) and E. dispar harmless
    - E. Bangladeshi
    - Etc. etc. many more to be found
- Epidemiology
    - Occurrence – 1 of three most common causes of death from parasitic diseases in the world.
    - Reseervoir – Humans
    - Transmission:
        - Travels using the Cyst through fecal-oral route/water/foodborne
        - Sexual transmission is possible (MSM at risk)
    - No Temporal Pattenr:
    - Communicability: 10-4 weeks
- Pathogenesis:
    - After ingestion of mature cysts, excystation occurs int eh smalle intestine. Trophozoites migrate to the large intestine and invade th walls there. They feed on RBCs, bacterial commensals and the wall of the bowel.
    - They also eat inflammatory cells and kill the bowel in a flask like shape (small opening, large hole).
    - Can spread to the liver through portal circulation, and either can occur, or both!
    - Immunity is incomplete. Thought to have igA immunity to Gal/GalNAc lectin preventing adherence.
- Clinical:
    - Intestinal:
        - Asymptomatic colonization (cyst passage)
        - Acute amebic colitis: 90% of symptomatic cases (i.e. regular pain)
        - Fulminatn colitis (really bad
        - Ameboma (They ate out uh, a lot)
    - Extraintestinal
        - Amebic liver abcess
        - Pleuropulmonary amebiasis (ew John's story)
        - Cerebral, Peritoneal amebiasis, Pericardial, genitourinary, etc.)
            - All depends on where it spreads and pierces thorugh
- Diagnosis
    - Stool analysis can reveal presence but cannot distinguish between species
    - Sigmoidoscopy or colonoscopy with biopsy/scraping of ulcer edges
    - Antibodies can help with non-intestinal diseases, where it doesn't appear in stool
- Treatment:
    - Asymptomatic/mild – Iodoquinol, parmomycin (luminal agents) + Diloxanide fuorate

    - Moderate + severe/extraintestinal – Metronidazole or Tinadazole followed by cyst treatment (luminal agents).
- Prevention:
    - Adequate sanitation
    - Clean water supply
    - Disposal of feces
    - Health education
    - Identification of carriers and treatment
    - Travel precautions (e.g. disinfection.)

Helminthic Enteric Infections

- Helminths can be divided into Nemotodes (roundworms) and Flatworms
    - Flat worms then get divided into hook worms (Cestodes) and Trematodes.
- Helminths are different from protozoa in that:
    - A) they are multi-cellular organisms
    - B) they TYPICALLY cannot multiply within the body (except strongyloides) This means that humans need to be repeatedly infected to actually develop disease.
- A subgroup of Helminths are the Geohelminths.
    - These are nematodes that transmit through soil, and require no intermediate host. Largely spread through fecal contamination of soils. Juvenile forms in the host, all species inhabit the intestine in adult stages and lay eggs in species.
- The typical lifecycle is:
    - Adult, egg (as you expect)
    - Larvae – two forms:
        - Rhabiditiform: Free living with muscular esophageal bulb.
        - Filariform – parasitic – slender, cannot feed, but can actually pierce through your skin and feed on a host.
- Transmission:
    - Through swallowing infective eggs/larvae via F-O
    - Through swallowing infective larvae in the tissues of another host (eating infected tissue)
    - Active penetration of the skin by larval stage
    - The bite of an infected blood-sucking insect vector.
- General Components:
    - One of the most prevalent infectious agents – #helm approx. = #people
    - A worm index has been developed, shows how it's inversely related to the country GDP – actually affects life!
- Life Cycles:
    - Simple Model:
        - Eggs passed with stools, becomes a larvae, feeds in the colon/cecum
    - Slightly more complex:
        - Two routes: Eggs passed with stools, then ingested eventually
            - Hookworm/Strongyloides, infected via skin penetration
        - Both routes migrate via the lungs to the small intestine

    - Most complex:
        - Eggs are passed through stools/sputum, then in intermediate hosts (e.g. aquatic animals/plants/snails), then ingestion of the intermediate hosts will get
    - Key things to remember: Lung migration: Strongyloides stercoralis, Necator americanus, Ancylostoma, **Ascaris Lumbricoides**
    - Two level – Fasciola Hepatica, Fasciolopis Buski and P. Westermani. Final site (Liver, Intestines, Lungs).
- Immune response – Relationship not exact, but Eosinophilia have shown to help in immunity with Schisto and Trichinosis. Largely the filariae, and thie schistosomes.

Ascariasis

- Agent: Ascaris lumbricoides:
- Epidemiology: Most common large worm pathogen worldwide
    - Reservoir – humans and pigs
    - Transmission – Fecal Oral, from contaminated food.
        - After ingestion – eggs mature, go through the lungs for 10-14 days, then penetrate through the lungs and down the throat. Once it hits small intestines adult worms live in the lumen of the small intestine. They then live in there for around 9-12 months.
    - Most prevalent in equatorial (73% Asia)
        - Esp. if uh, night soil (feces) is used as fertilizer
    - Infection peaks at 10 year old ages.
- Survivability – Eggs are VERY robust (layers, coated with mucopolysaccharide).
    - 2 years at 5-10 C in absence of oxygen
    - Dessication for 2-3 weeks
    - Survives in cold 5% formaline
- Clinical:
    - Most infections asymptomatic, dependent on worm burden + organs
        - Intestinal : mild GI upsetness to intestinal obstructions
            - Nausea, vomiting, diarrhea, obstruction, bile/pancreas obstruction leading to itis.
        - Nutritional – contrigbute to neg nitrogen balance in children
            - Malnutrition, malabsorption
        - Pulmonary: Loeffler's Syndrome
            - Seen during migratory phase (i.e. when they pass through lungs)
            - 1-2 weeks after ingestion of eggs
            - Caused by hypersensitivity to larvae, typically due to larvae
- Diagnosis – extremely high egg output (200k eggs/per worm/day)
    - Poop smear! Lots of high eggs.
- Treatment:
    - Single dose oral therapy with albendazole/mebendazole. Pyrantel pamoate in pregnancy. Worm removal if obstruction.
- Prevention:

    - Mass treatment of high risk rate per (3/4 years), Improving hygiene and sanitation/Reducing poverty Education/health awareness

Hookworm

- Etiology: Two major agents: **Necator americanus and Ancylostoma duodenale**
    - Occurrence: New world hooknorm vs North Africa/North India China
    - Both agents can hatch into rhabiditiform larvae for soils urvival. Filariform larvae can live in soil for up to 2 years
    - A. Duodenale produce 30k eggs, N. Amercanus 9k eggs daily
- Epidemiology:
    - Occurrence: 740 mill worldwide, Africa > China > SEA
        - 65 deaths/year world wide
        - Majority of individuals are low level infections (65-85%)
        - Hookworm prevalence is largely in South America, Africa, China/SEA.
        - All ages: prevalence increases with age (plateaus at 25)
- Pathogenesis:J
    - Eggs passed in stool, larvae hatch in 1-2 days. Rhabidiform larvae grow in feces/soil, 5-10 days later becom filariform that can actually infect. 3-4 weeks in favourable situations. They penetrate and carried through blood to lungs, penetrates through aveoli, swallowed through intestine. Larvae hit small intestine, attatch to lumen, lay eggs!
    - A. Duodenale can just be F-O too, but N. Americanus must pierce.
    - Blood loss can occur when the adult worm fastens onto the intestinal wall with its teeth/cutting plates (duodenal vs americanus). This can cause anemia.
        - Sucks (contracts esophagus) to rip out part of intestine
        - Release of proteases for fibrinogen
        - Parasite-devrived anticoagulants
    - IDA – due to type of hookworm, worm burden, iron reserve
- Clinical:
    - Can be asymptomatic, acute (dermatitis, pulmonary Loeffler's), or abdominal
        - Acute dermatitis typically at the point of entrance
        - Abdominal pain, nausea, vomiting, diarrhea, flatulence (all correlate with larvae migration.
    - Chronic symptoms include: Anemia, hypoalbuminemia, growth retardation
- Diagnosis: - Pop smear again!
    - However, you can get a false negative through fresh stool samples.
- Treatment – albendazole single dose, Mebendazole or pyrantel pamoate 3x. Iron replacement therapy.
- Prevention:
    - Mass treatments again. Requires consistent treatmenet (4-12 months till next infection), can increase drug resistance.
    - Sanitary disposal,
    - Health education, esp footware and cooking
    - Possible vaccine to Necator Americanus!

Strongyloidiasis

- **Etiology:** Three important differences between S. stercoraliosis:
  - **Larvae are passed in stool**
  - **Autoinfection:** It can develop into filariform larvae in the host, thus increasing worm burden
  - **Free-**living life cycle: It can also develop outside the human host in soil
- **Epidemiology:**
  - **Less common than other helminths, 70-100 million, 80% in Sub-saharan Africa**
  - Endemic to tropical and subtropical countries
- **Pathogenesis:**
  - Free living cycle: Rhabidiform larvae passed in the stool, can become filariform/free living males/female that make eggs
  - Parasitic cycle: Filariform larvae can infect skin, through various routes, migrate to the small intestine. (thought due to lungs initially, but now also through connective tissues. Mature into femlaes, and produce eggs, which go to rhabidiform larvae. Either are shed (to free living cycle) in stool or develop into filariform larvae which can auto-infect.
    - This auto-infection can occur in immunocompetent individual. Allows for persistent infections.
- **Clinical:**
  - Wide range of symptoms: Mild GI complaints/asymptomatic.
  - Acute infection: Papular rash at site of entry (usually in feet or butt), Rare pulmonary symptoms, or Gastrointestinal disease (Epigrastic pain/diarrhea/anorexia, nausea, vomiting)
  - Chronic: 1/3 assymptomatic, you can have larva currens (running track.
    - GI – abdominal pain, intermittent diarrhea, malabsorption, Anorexia, Nausea/vomiting, Gi bleeding
  - Hyperinfection – When the infection exponentially increases. Filariform larvae penetrate the intestine/mucosa and allow for bacteria to hit the bloodstream,
    - Risk factors – immunodeficiency, steroids, Malnutrition, alcoholism
- **Diagnosis:**
  - Stool ova/parasite examination You should see larvae
    - It's sporadic so you don't necessarily see it
    - Sampling upper GI secretions
    - Serology
    - Culture
- **Treatments:**
  - **Treatment of all patients:**
    - Ivermectin (1 does 64%-100%)
    - Alvendazole (3-7 days)
- **Prevention:**
  - Improve fecal sanitation
  - Education, Shoes

- Diagnosis of at risk individuals, esp. before immunosuppressant administration.

Schistomiasis BLOOD FLUKE

- Schistoma spp.
- **How does understanding the life cycle of this organisms inform your understanding of**
  - **The clinical manifestations**
    - **The eggs and the flukeworm affect the pathogenesis**
  - **How to prevent human infection**
    - **Gotta prevent the feces from getting into the water and the water from getting to the people**
- **How does the host's immune response allow for the transmission of the worm?**
  - **Absorbve host proteins and coat themselves with host antigens (evade for years!)**
- **Eitiology:**
  - 5 species that infect humans:
    - Main species : Mansoni, Japonicum, Hematobium
    - Others: Merkongi, Intercalatum
- **Epidemiology:**
  - Occurrence
    - Mainly sub-Saharan Africa for Mansoni/Hematobium
    - East asia /SEA for Japnoicum
    - 700 mill at risk, 240 mil infected worldwide, 120 mil of each have symptoms., 20 mill has sever disease
    - 800k deaths per year
    - Two factors for endemicity
      - geographic distribution of the snail
      - Method of urine/feces disposal
    - Life Cycle: Through urine/feces, the three types hatch in water, infect snails, generate sporocysts in snails over a couple of generations, then release into the water, and penetrate skin. Within the skin, they lose their tales and circulate as schistosomulae, and migrate into the liver. They mature and then hit their end stage. location
  - Transmitted through fresh water – life cycles rely on snails, and they penetrate skins.
  - Risk factors – age – prevalence increases with age
  - Reservoir: Humans primarily, there are animal reservoirs for mansoni and japonicum
- **Pathogenesis**:
  - They live in veins, lock together and mate for life (up to 30 years!)
  - End stage depends on strain, venules/veins of:
    - Mansoni: colon, Japonicum, small intestines
    - Japonicum: Mesenteric venules of the small intestines

        - Haematobium: Vesicular venous plexus
    - The eggs produce travel hematogenously + through vein wall to the target organ, can invade tissues, cause immune response (granuloma)
    - Adult worms can also absorb host proteins and coat themselves with host antigens – "camouflage". Works for years.
- **Clinical:**
    - Immediate: Swimmers Itch (from where it infects) lasts for a few days.
    - Acute response: Snail fever (Katayama fever) – serum sickness like reaction. Fever, headache, pain, bloody diarrhea, cough, etc. Few weeks.
        - Starts when paired worms begin egg production. Thought to be due to immune response to both the migrating prasites or the antigens in the eggs
    - Chronic:
        - Chronic schistomiasis can work in intestinal, urinary, and female genital. Most infections are asymptomatic.
        - Can lead to anemia, growth retardation, chronic fatigues, learning difficulties
        - Intestinal – mansoni/japonicum typically
            - Chronic pain/poor appetite, diarrhea, due to polyps/ulcerations in the colon
        - Liver: mansoni/japonicum
            - Portal tract fibrosis
        - Urinary: Haematobium
            - The eggs get deposited at the lower end of the ureter and in the bladder wall, most infeted with haematobium are symptomatic.
            - Causes urinary tract obstructions, urinary frequency, painful urination, hematuria
            - Can cause renal failure, bacterial infections, cancer
        - Female Genital- haematobium
            - Ulcerations of femal reproductive tract
        - CNS – Japoicum 4%, rare in haematobium/mansoni. Usually in brain/spinalcord.
    - Diagnosis:
        - Katayam fever, Rectal bleeding, Hematuria, hematemesis
        - Eggs in stool or urine 6-8 weeks after infection, or from biopsy
        - Serology for non-endemic populatios
        - PCR, Imaging
    - Treatment: Praziquantel (increases Ca, immobilizes worm, paralysis) Cure-rate 85%. Artemisinin has rapid onset of action, seems rpettyg ood against mansoni/japonicum.
    - Prevention: improve water sanitation, eliminate snail intermiedate hosts, decrease contact with fresh water. Mass treatment with anti-helminth agents. Traveler education.
        - Elimination is difficutl due to animal reservoir

- Global wwarming (warmer temperatures + decreased water availability = BAD)
-

Respiratory Infectious Diseases

How does droplet size influence transmission? Aerosol / Droplet Nuclei – Is airborne for up to several hours, with various evaporation actors making them smaller! Their small size (sub 5 micron) makes it easy for them to stay suspended – they effectively never drop – Central HVAC can spread it too! If someone in the very back of a stadium!!!!! Measles or TB – negative air flow
Medium-large Droplet – Don't stay suspended in the air – range 3-6ft (exact range unknown?)
Why do we need to know this? It informs us on how to prevent spread
Also, this changes the types of disease: Large Droplets can't make it all the way to the end of the lung largely URI, nuclei are can make lower respiratory infectious.

What are host defense against respiratory pathogens?

- Mucociliary transport mechanism
- Epithelial barrier
- Respiratory mucus
- Local production of immunoglobulins by plasma cells (largely IgG and IgA)

What are bacterial counter-strategies to evade host defenses in the respiratory tract?

- Affinity for mucus/cilia
- Pili that promote adherence
- Secretion of proteolytic enzymes that break down local immunoglobulins

What impairs host defenses of the respiratory tract?

- SmokingL: destroys cilia and their function, increase in mucus production
- Inhaled pollutant or dust: exposes more epithelial cells through damage
- Impaired cough/gag reflexes (e.g. age/drugs(narc + alcohol))
- Obstruction
- Advanced age

What defines community acquired pneumonia (CAP)?

- Acute infection of the lungs in person who have not been hospitalized recently/not had regular exposure to the health care system.

What are some common pathogens of CAP?

- Influenza
- Strep Pneumonia - pre antibiotics, 95%, post, 10-15%
- Haemiphilus Influenzae
- Staphylococcus Aureus

For what respiratory pathogens are there safe and effective vaccines?

- Influenza
- Haemophilus Influenza type B
- Pneumococcus
- Pertussis
- Adenovirus
- Diphtheriae

Influenza

What happened in 1918?

1918 had a notable H1N1 influenza epidemic (the infamous Spanish Flu). >500k killed in the US, 20-100 million killed world wide. In comparison to 9.2 million combat deaths, it was absolutely devastating.

It is thought to be from some sort of recombinant virus originating in a pig. Most people tended to die from secondary pneumonias caused by other bacteria.

There wer ea lot of deaths among the young and healthy – Swartzberg's lecture mentioned that young people were shipped around in training camps all over the US (i.e. crowding, spread), and were sent afterwards to war and infected others! So lots of death among that demographic.

The three pandemic waves seemed to indicate a "harbinger" wave – that a small pandemic presaged the larger pandemic wave during the end of 1918. This was disproved in future waves.

We're able to do better now with antibiotics, antivirals, better medical care, and better public health – preventative vaccines also help a lot!

How does the structure of influenza inform our understanding of the epidemiology?

Two important surface markers, HA and NA serve as a) the markers for outbreaks (sequencing the genes that make this), and b) the virulence factors (they do adhesion/penetration and capsule release respectively). The capsule itself (M1) is a little important.

How do we classify the influenza virus?

We classify using the HA and NA subtypes, noting H1-18, and N1-11.

Who (and how many) get infected? Who dies?

The reservoir for these disease are in avians, pigs, humans, bats, and other animals! Plenty! Birds are notorious given the common practice of rearing them in extremely dense conditions.

Different behavior in A vs B cs C:

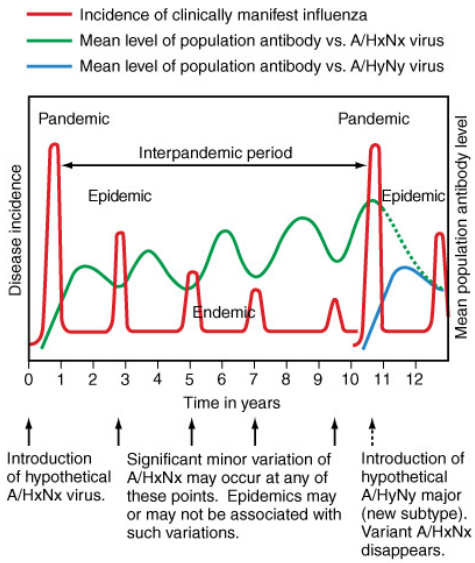
	Influenza A	*Influenza B*	*Influenza C*
Genetics	8 gene segments	8 gene segments	7 gene segments
Structure	10 viral proteins M2 unique	11 viral proteins NB unique	9 viral proteins HEF unique
Host range	Humans, swine, equine, avian, marine mammals*	Humans only	Humans and swine
Epidemiology	Antigenic shift and drift	Antigenic drift only; two main lineages cocirculate	Antigenic drift only; multiple variants
Clinical features	May cause large pandemics with significant mortality in young persons	Severe disease generally confined to older adults or persons at high risk; pandemics not seen	Mild disease without seasonality

*Recently, influenza viruses have also been isolated from dogs and cats.
HEF, hemagglutination, esterase, and fusion activity; NB, membrane protein.

More specific epidemic information:
1 billion infectinos, 3-5 mill severe, 291k-646k deaths due to influenza each year.
Simialr numbers in US (20-50 million cases, 55-431 hospitalizations, 3349-48614). Morbidity and mortality rates are highest in people in the lower socioeconomic strata + elderly people.
80k deaths last year.

How does population immunity influence epidemics and pandemics?

Usually, a pandemic occurs, and many people start developing more antibodies. This decreases (from pan to epi to en) until a new Hx/Nx strain is introduced, at which a pandemic occurs again.



How is influenza spread?

Influenza is spread through typically medium size and droplet nuclei. Asymptomatic infection is unusual (<1/3) and viral shedding occurs for 5-7 days.

Air planes seem to play a huge role e.g. 3 hour HK-Beijing flight, passengers sitting within 7 rows of an "index patient" developed SARS.

How does the cytokine storm affect the pathogenesis of Influenza?

- Cytokine storm: Influenza viruses are potent inducers of many biological response mediators that make up the innate immune system. During acute infection increased serum levels of several proinflammatory cytokines (e.g. TNF-alpha and IL-6) have been positively correlated with the signs and symptoms of clinical illness ("cytokine storm").

Is it the flur or a cold?

Symptoms	INFLUENZA	COMMON COLD
Onset	Abrupt	More gradual
Cough	Common, severe	Mild to moderate
Malaise	Severe	Mild
Fever	Common—100°-104°F	Uncommon or only 1°F increase
Myalgia	Severe, common	Uncommon
Arthralgia	Severe, common	Uncommon
Anorexia	Common	Uncommon
Headache	Severe, common	Mild, uncommon
Prostration	Early & prominent	Rarely
Chest discomfort	Common, severe	Mild to moderate
Stuffy nose	Occasional	Common
Sneezing	Occasional	Common

How does influenza kill?

It kills typically through secondary bacterial pneumonia.

How do our durgs work?

Neuraminidase Inhibitors (NIs): Oseltamivir and Zanamivir: They block viral adherence and penetration to the host mucosa and the release of formed viral particles. Normally, the neuraminidase, a sialidase, facilitates release by cleaving receptors on the cell surface. In the presence of a neuraminidase inhibitor, release is restricted, and the progeny viruses that are freed clump together. [Caveat: Reviewers with financial conflicts of interest may be more likely to present evidence about NIs in a more favorable manner and recommend the use of these drugs than reviewers without financial conflicts of interest. AIM 10/7/14. But, there is evidence that NIs are underutilized by US physicians. CID 9/15/14]

How can we prevent Influenza?

Prophylaxis

- Cover your cough.
- Six foot rule (with a caveat)

- Voluntary home quarantine
- Social distancing
- School dismissal
- Mask for cases when necessary (as of 2010 the CDC recommends surgical face masks instead of the N-95 respirator for healthcare workers during all contact with influenza patients)
- Mask when caring for cases
- Hand hygiene: perhaps helpful (very little data to support this)
- Antiviral treatment of index case
- Household antiviral prophylaxis: no empirical data
- All HCW's should be vaccinated or wear a mask when working
- Oseltamivir ring prophylaxis for containment of outbreaks (NEJM 6/10/10)
- Oseltamivir significantly reduces complications from influenza and therefore the need for antibiotics
- Interventions depending upon pandemic severity index:

• **Intervention by setting**	**Severity index 1**	**Severity index 2 and 3**	**Severity index 4 and 5**
Voluntary isolation at home combined with use of antivirals as available and indicated	Recommended	Recommended	Recommended
Voluntary quarantine of household members in homes with ill persons; consider antiviral prophylaxis	Generally not recommended	Consider	Consider
Dismissal of children from schools and school-based activities, and closure of child care programs	Generally not recommended	Consider	Recommended
Reduce out-of-school contacts and community mixing	Generally not recommended	Consider: ≤ 4 weeks	Recommend: ≤ 12 weeks
Adult social distancing: decrease number of social contacts	Generally not recommended	Consider	Recommend
Increase distance between persons (e.g. public transit, workplace)	Generally not recommended	Consider	Recommend
Modify, postpone, or cancel selected public gatherings.	Generally not recommended	Consider	Recommend
Modify workplace schedules and practices (e.g. telework, staggered shifts).	Generally not recommended	Consider	Recommend

Vaccines are good! – matches between vaccine and field strains can be eh but always good to vaccinate. The process of vaccine productions: Select viruses to vaccinate against in February/September for NH and produce for 6 months. Then administer

Mumps

Eitiology

- Single serotype, from Paramyxoviridae. Contains a helical core (genomic portion) + glycoprotein envelope. Surface proteins allow for hemagglutination neuraminidase activity + cell fusion.

Epidemiology

- Occurrence: Endemic around the world, we need ~90-92% popn immunity for herd immunity. Used to be bad but Mumps vaccine introduce 1967. UC Berkeley had a case in 2011, hit 44 peeps.
- Reservoir: Humans only
- Transmission – droplets of saliva and mucus, typically through coughin, sneezing, talking. Dirty surfaces
- Incubation ~ 12-245 days
- Temporal – Winter-Spring peak
- Commnicability – Highes irates are around parotitis onset and the subsequent 5 days.

Pathogenesis:

- Replicates in nasopharynx _+ lymph nodes. Viremia occurs after 12-245 days, then inflames various tissues (mininges, glands).

Clinical:

- 20-40% asymptomatic, up to an extra 40-50% are largely respiratory.
- Most common manifestation is Parotitis
- Complciations: Other glandular tissue, pancreatiss, meningitis, etc. all can happen

Diagnosis:

- Clinical diagnosis of parotitis
- Serology of IgG and IgM, around 3 dfays after symptoms.
- Reinfection can happen.

Treatment:

- Supportive

Prevention – immunization

- Vaccines are about 62-91 effective for one dose and 76-95% for two doses. US + Canada have it in their infant immunization schedule. (MMR)
- Issues with the vaccine – without natural boosting (i.e. endemic exposure to the disease) efficacy of the vaccine wanes to the lower limits above. This hinders general immunity.

Diphtheria

Acute infection of the upper respiratory tract or a cutaneous lesion.

Eitiology:

- Part of the genus Corynebacterium, with 3 notable species:
- C. Diphtheria (largely human, cause of outbreaks), C. ulcerans, C. pseudotuberculosis (zoonotic)
- Non sporulating, unencapsulated, nonmotile, pleomorphic Gram positive bacillus
- Toxin is phase-encoded, requires a lysogenic prophage to actually produce.
- Four stable biovars, used for epidemiological purposes

Epidemiology:

- Occurrence – occurs worldwide but more common in temperate zones. Used to be > 200k cases. Drops to 0 in US by 2004.
    - 90% of cases in South/Southeast Asia, with some areas in Haiti

    - Also very common among the poor, with decreased immunization, hygiene, crowding
- Reservoir – Humans for C. Diphtheriae, Cattle for ulcerans.
- Temporal – Winter/spring
- Transmission – Nasopharyngeal secretions, droplets. commonly via droplet spread. Also, Direct contact (the most common route)
- Communicability – Incubation is 2-4 days on avg. Carrier state may exist for a logn time. Transmission occurs from 2 weeks or less, rarely longer than 4 weeks.
    - With antibiotics, shedding immedaitley stops.

Pathogenesis:

- The diphtheria exotoxin causes the death of eukaryotic cells.
    - Low iron + lysogenic prophage is conducive for C. Diphtheriae to actually produce toxin. Prophage encodes on a repressor signaled by iron, so we require both the prophage to be there and the repressor to be inactive.
- Infection can start with non-toxigenic, then toxigens can be created once the lysogenic prophage is actually activated.

Clinical:

- Symptoms – local noninvasive infection in skin/respiratory tract, or distant tissues through toxin dissemination. 5-10% people die . Most commonly mortaltity due to diphtheritic cardiomyopathy, suffocation by psuedomembrane, renal failure.
- Deaths mainly in young <5 and people > 40. Tuberculosis
- Host response Virulence, and location of infection all affect the lcinical presentation

Diagnosis:

- Clinical symptoms above
- ≈
- PCR
- Serology

Treatment

- Diphtheria Antitoxin (DAT) – we derive this from horses!. Sometimes causes a rxn.
- Penicillin/erythromycin (reduces spread of local infection, reduces transmission, reduces toxin formation)
- Airway managmenet
- Cardiac + neurologic monitoring

Prevention:

- Vaccination (toxoid vaccine):
    - Given with tetanus in either DT or Td formulations (strong/weak diphtheria contribution). Also given as part of Tdap
- Post exposure prophylaxis
- Hospital isolation

Tuberculosis

- There is still no good vaccine drug, or diagnostic test for TB

Epidemiology:

- **Describe the agent of TB and how it is transmitted**
  - The pathogen is *Mycobacterium tuberculosis*, and it is transmitted through airborne droplets.
  - Settings of transmissions: Congregate settings: Nosocomial, Prisons, School, Homeless shelters, slums
  - Transmissions increased by: index cases, index cases with cavitary pulmonary disease, among close contacts, with long duration/freq of contact.
- **Name 5 countries with the highest incidence of TB.**
  - India, Indonesia, Nigeria
  - US: NYC, DC, Illinois, California, Texas, Florida, and a couple of others
  - Occurrence: 10 mill incidence. It's largely in sub-saharan Africa + SEA.
- **List groups at high risk for TB in the US**
  - Older people
  - Asian and Pacific Islanders
  - African American
- **Describe three recent trends in TB incidence in the US**
  - Decreasing trends amongst US born citizens
  - Increasing rates amongst native Hawaiian islanders
  - Increasing rates amongst non us born persons e.g. in Texas and florida
- -Overall rates of TB (rate of incidence in most states)
- -TB stratified by race (looking at Asians and Native Hawaiians/Pacific Islanders)
- -Tb stratified by whether individuals were born in US or born outside of US (% of cases in each group)
- -Which states have the highest burden
  -
- **Describe characteristics of a TB patient or conditions that increase the probability for transmission**
  - Coughing, Cavity in lung, TB of the lungs/airway/larynx, Patient not covering mouth/nose while cofing, not receiving treatment, undergoing cough-inducing procedures
  - Crowded conditions.

Microbiology/Clinical Spectrum

- **Describe the microbiologic characteristics of *M. tuberculosis* that distinguish this organism from other mycobacterial organisms**
  - Its characteristic cell wall is unusually smooth, and has the mycolic acid.
  - The other major one we should care about is bovus
- **Describe the 3 main outcomes of infection following exposure to the agnet of TB**
  - Immediate clearance (70%)
  - Latent infection (18%)
  - Primary active disease (12%)
- **Describe the difference between TB and latent TB infection (LTBI)**
  - Latent is when they don't show any symptoms. Not infectious.

    - Primary active tuberculosis shows immediate symptoms
- **List groups at high risk of progressing to active disease from having LTBI**
    - People with weakend immune systems (e.g. HIV, diabetes, immunosuppressant)
    - Children younger than 5 years of age
    - Low body weight
    - Smokers/Alcohol/Drug users
    - Recent TB infection (2 years)
- 8. I can't say for sure that this slide is going from most susceptible to least susceptible, but definitely HIV co-infection would probably come first, followed by diabetes and then followed by other conditions that may cause a less severe immunocompromised state.
-
    -
- **Define multidrug-resistant TB (MDRTB), extensively drug-resistanct (TB)**
    - MDR-TB – TB caused by M. tuberculosis resistant to isoniazid and rifampin
    - XDR-TB – TB caused by M. tuberculosis resistant to isoniazid, rifampin, any fluroquinolone, and at least one of three injectable second-line drug (capreomycin, kanamycin, and amikacin)
    - Primary vs Acquired drug resistance – was resistance acquired before or after infection
    - The most common places are former USSR countries.
- **List 3 factors that contribute to the selection of drug-resistant TB**
    - Drug resistance is caused by point mutations in a small number of genes (katG,k rpoB, pncA, etc.).
    - Risk factors: High baccilary load
    - Inappropriate or inadequate treatment (e.g. only one drug. Usually at least 1 or both drugs).
    - Poor or non-compliance with treatment
    - From review (poor hygiene, being poor)_

Immunology and pathogenesis

- Describe the steps that *M. tuberculosis* takes to establish latent infection
    - M. Tuberculosis enters an aveolus
    - It attatches onto Aveolar epithelial cells type I and II (the thing ones and the secretory ones).
    - Macrophages react to the M tuberculosis
    - T-cells then surround the macrophages, fully forming a **Granuloma**, protecting the *M. tuberculosis* against the host.
- Describe recognized *M. tuberculosis* factors that subvert or resist host response to *M. tuberculosis*
    - They can subvert innate response by:
        - TLR-2 inhibition of inflammatory response by the mycolic acid
        - Disruption of phagosome maturation
            - Inhibition of phagosome lysosome fusion
        - Inhibition of acidification
        - Resistance to ROS and RNS (nitrogen)

        - Escape into cytoplasm from phagosomal compartment.
    - They can subvert acquired response by:
        - Induction of the delayed adaptive immune response
        - Decoy antigens that can compete against antigens that activate effector T cells
- Name host immunological factors recognized to keep *M. tuberculosis* in a latent infection state
    - T helper cells help maintain the granuloma, protecting the host and the bacteria
    - CD_4+ T cells might help with not having reactivation TB (loss has been associated with reactivation TB).
    - Exact mechanisms not necessarily known, but often triggerd by changes in host immune status.
- 6. Yes definitely helper T cells are important. I would also consider the roll of TNF alpha and TNF alpha receptors in the maintenance of these granulomas. TNF alpha is produced in response to certain infections. In the immunology of reactivation slide, it notes that when TNF alpha and TNF alpha receptors are inhibited, this can trigger reactivated TB.
-
    -
- **KEY NOTE: NO CORRELATES OF PROTECTION**

Diagnosis of TB and LTBI

- Name 3 standard tests used to diagnose TB.
    - TST
    - Culture (First cultured by Koch)
    - IGRA
    - Microscopy
    - Chest X-ray?
    - Growth based assays
    - Serologic tests (Like TST and IGRA)
    - Nucleic acid amplification (NAAT).
- Describe the limitations of microscopy used to diagnose TB
    - Issue Ziehl Neelsen stain requires heating
    - Also, you need 10^4 organisms/ml for detection
- Name 2 test used to diagnose latent TB infection (LTBI)
    - TST
    - IGRA
- Explain the immunological mechanism behind gamma-interferon release assay (IGRA).
    - Synthetic antigen specific to *M. tuberculosis* vs BCG (CFP10, ESAT-6, TB7.7) are produced
    - Blood is drawn, miaxed with antigen and control processes, and immune cell response to the IGRA are read out
- Name 3 advantages and 2 disadvantages over the tuberculin skin test
    - Pros: Doesn't react to BCG, people don't have to come back, interpretation may be less subjective

    - Cons: Expensive, test needs to be carried out within 12 hours of blood withdrawal. May cross react with other strains (less common)
- Describe situations in which IGRA can be used as recommended by the FDA
    - When the patient is unliekely to return
    - When the people who have had BCG immunization
    - When the person is >= than 5 years old

Treatment and Prevention

- Name 3 first line drugs used to treat TB
    - Isoniozid - INH
    - Rifampin – RIF
    - Ethambutol
    - Pyrazinamide
    - Second line – Cycloserine, Cirpoflaxosine, Bedaquiline
    - Preventative for LTBI is just Isoniozid or Isoniozid +rifampin.
- Name one major difference in the control programs of the US vs those of developing countries
    - US control programs involve preventative treatment for LTBI, where index cases and new infections are monitored closely and their contacts monitored and treated.
        - This is bc disease incidence is low and we can monitor where outbreaks might happen from
    - Abroad:
        - Since BCG is given and disease incidence is high, TB preventative for LTBI is not easy or great
        - However, they just give broad protection against disseminated TBI.
- Explain the purpose of the US TB contact investigation program
    - The contact programs as follows:
        - Identification of active disease
        - Evaluation of the contact cases for TB cases and provision of treatment for them
        - Use target testing strategies to identify and treat persons with LTBI at risk for reactivation
        - Identify settings at high risk transmission of *M. tuberculosis* and apply effective infection-control measures
    - It: Helps interrupt the spread of TB, prevents TB among contacts, prevents outbreaks of TB, and ensures appropriate treatment for LTBi or TB disease
- Describe situations in which it is necessary to initiate a contact investigation
    - In confirmed TB cases, with a full one CI is required for all confirmed cases for infectious forms (Lungs, airway, larynx TB)
    - In suspect cases for positive sputum smears + NAAT positive tests, or cavities on chest x-ray
    - Not necessary if NAAT test returns negative, non-infectious TB (extrapulmonary), or is a child < 10 years of age.

- Describe how one assesses LTBI during a contact investigation
    - TST or IGRA – if pos, examine for TB, if neg, retest 8- 10 weeks after last exposure (The window period) – you need 2-10 weeks to actually mount a detectable
- Describe how one makes a decision to treat a contact diagnosed to have LTBI
    - People infected with HIV, Children , 5< yrs of age who are household contacts of pulmonary cases of TB
- On BCG:
    - BCG only protects against disseminated TB in children
    - But does not really protect against pulmonary TB and reactivation for TB
    - Overall effectiveness about 50%
- DOTS – the WHO strategy ofor TB control
    - Detect the case through a quality lab
    - Standardized treatment WITH supervision and patient support (you have to SEE them take the drugs)
    - Monitoring and evaluation system and impact measurement
    - Effected drug supply/management system
    - Political commitment with increased sustained financing.

Other Respiratory diseases

Haemophilus Influenza

- Describe the defining biochemical characteristic of *Haemophilus influenza*
    - Requires both Hemin and NAD to grow
- Name the spectrum of clinical manifestations caused by *H. influenza*
    - Meningitis, ottis media, sinusitis, epiglottitis, tracheobronchitis, pneumonia, bacteria
- Describe the immunological correlates of protection against invasive *H. influenza* disease
    - Type specific antibodies against polyribosyl ribitol phosphate capsules. (anti-PRP

Group A Streptococcus (*Stretococcus pyogenes)*

- Describe the sub-classification scheme for Group A streptococcus (GAS)
    - Subclassification is done via the M and T proteins (which are its serotypes)
    - You can also classify it based on the emm gene (which encodes the M protein)
    - >100 M types, 20 T types, > 170 emm gene types.
- Describe the spectrum of diseases caused by GAS
    - Upper reswpiratory infections, skin infections, necrotizing fasciitis (flesheating infection), toxic syndromes like scarlet fever,.
- Name the toxins expressed by GAS
    - Streptolysin O and S
    - Streptococcal pyrogenic exotoxins aka erythrogenic exotoxin (superantigens responsible for scarlet fever and toxin shock) (phage mediated.
- Describe the 2 sequelae of GAS infections

    - Rheumatic heart disease (damage to the heart valves after Acute Rheumatic Fever, identified from various symptoms (carditis, arthritis, subcutaneous nodules, chorea (dancing disease, involuntary tics).
    - Glomerulonephritis (acute inflammation of the kidneys, caused by immune complexes on glomeruli)
- Issues on creating an emm vaccine:
    - The emm distribution varies according to location, so impossible to protect against all of them.
    - We treat with prophylaxis anyway.

Streptococcus pneumoniae (Pneumococcus)

- Describe the main microbiologic feature of Pneumococcus that gives it a unique characteristic in the context of diagnosis, immunology, and pathogenesis
    - The capsule is largely individualized, and forms the basis of the pathogenesis and for the vaccine itself. It reacts to optochin (drug), and undergoes the quelling reaction, where the capsule swells due to antibody
    - Produces α-hemolysin whgich breaks down hemoglobulin into a green pigment.
- Understand the epidemiology of CAP caused by Pneumococcus
    - 20-40% of CAP caused by pneumococcus (bacteremic + non-bactermic).
        - Risk popns – indigenous people, males, HIV, diabetes, African American children, extremes of ages
        - Complications of influenza/measles
- Describe the challenges that need to be overcome to develop an effective vaccine against CAP caused by Pneumococcus
    - The big issue is that there are a crazy amount of capsule types (serotypes). So we can only protect against so much – 23-valent polysaccharide cvaccine, and two conjugate vaccines (7-=valent, 13-valent) most common.
    - **Conjugate important bc… (Look it up as soon as you see this)**

The common cold

- **Name the 6 categories of upper respiratory infections (URI)**
    - Common cold
    - Pharyngitis
    - Sinusitis
    - Otitis media (middle ear infection)
    - Tonsillitis
    - Tracheatis
- **Identify the top 5 causes of common cold**
    - Rhinovirus, Coronavirus, RSV, Adenovirus.
- **Describe the mechanisms of URI caused by rhinovirus**
    - Uses the same ICAM-1 receptor as WBCs to infect respiratory cells. Induces a cytokines and contributes to recruitment of inflammatory cells.
- Rhinovirus – infects via the ICAM
- Coronavirus – Transmits in the same way, corona is made of proteins that help it bind to other places
- Adenovirus – doublestranded DNA, >50 serotypes.

SARS:

- General timeline:
    - **305 cases in guandong Province**
    - Professor treated atypical pneumonia in Guangzhou hospital
    - Visited hotel in Kowloon, developed SARS, died in local hospital
    - 7 others of the same floor developed similar symptoms, 2 died
    - Local cases admitted to Prince of Wales Hospital, 100 staff developed same disease
    - Outbreak in HK
    - WHO and CDC issue global alert
    - 264 cases in 11 countries
    - Index cases traveled to Ireland, Canada, US, Singapore, Vietnam,
- Electron microscopes of SARS revealed that it was a coronavirus, but we had to PCR it (couldn't culture it). It had a different genome
- Transmitted from Civet to person, Person to person, and from fomites – up to 24 horus after contaminated surfaces.
- Huge issues – Airbornes and aerosolization in hospitals – HCWs weren't protected since they weren't wearing N95s.
- Thought to have been cultured in Bat reservoirs, transmitted to civets, then eaten.
- Diagnosed via RT-PCR, serlogy, or cell culture.
- Treatment through supportive treatment and sterile environments
- Prevention via Infection control in hospitals (N95, negative control, quarantine).

PH260A Final Review

K. L. Barry Fung – 2018-12-04

DR. SWARTZBERG'S SECTION

1. *Chlamydophila pneumoniae*
    a. For your consideration:
        i. What human diseases are caused by *Chlamydia* and *Chlamydophila*?
            - *C. trachomatis*
                - Serovar A-C in eyes, causes conjunctivitis
                    i. Long term - blindness
                - Serovar D-K in general nether regions , causes nongonococcal urethritis, cervicitis, proclitis (rectum and anus)
                    i. Long term – Pelvic inflammatory disease
                - Serovar L1-L3 in genitals/lymphocytes, causes genital ulcers + lymphadenopathy
                    i. Long term - Rectal scarring, lymphatic fistulae
            - *C. pneumoniae*
                - Upper respiratory infection, community acquired pneumonia
                - Possibly LT: CVD
            - *C. psittaci*
                - CAP, long term hepatitis
        ii. How does C. pneumoniae's life cycle relate to its pathogenesis?
            - The life cycle is:
                - (1) elementary body is endocytosed
                - (2) prevents fusion of phagosomes + lysosome
                - (3) differentiate and reticulates
                - (4) can actually stay dormant based on presence of immune response, (IFN -γ)
                - (5) when immune response is removed or there is none, it matures, redifferentiates into elementary bodies, lyses the cell and spreads further to repeat
            - The big thing to get is that it actually is able to survive immune pressures as a latent infection.
            - Also, it's an obligate intracellular pathogen
        iii. What is meant by "atypical pneumonia?"
            - Atypical pneumonia is pneumonia not of the normal pathogens (i.e. streptococcus pneumoniae), which is typically less strong
    b. Review Questions:
        i. Why are beta lactams not used for treatment of C. Pneumoniae?
            - My guess is that b/c it's intracellular and there are issues but I also cannot tell.

ii. Why is the pneumonia caused by C. Pneumoniae described as “walking pneumonia”
    - See the above
iii. What is the reservoir of C. Pneumoniae?
    - Humans only.
iv. Is the reticulate or elementary body the infectious life stage of C. Pneumoniae?
    - Elementary body, reticulate ONLY occurs intracellularly
v. Is immunity acquired to C. Pneumoniae during infection long lasting?
    - Nurp

c. Full Analysis using the Swartzburg framework:
    i. Etiology:
        - This is an obligate intracellular pathogen, which requires another cell to actually replicate and live!
        - Chlamydia actually has four distinct families but we’re lazy
        - C. Pneumoniae is genetically distinct from the two other major species, and within the species all strains are immunogenically similar.
        - The life cycle copied from above is:
            - (1) elementary body is endocytosed
            - (2) prevents fusion of phagosomes + lysosome
            - (3) differentiate and reticulates
            - (4) can actually stay dormant based on presence of immune response, (IFN -γ)
            - (5) when immune response is removed or there is none, it matures, redifferentiates into elementary bodies, lyses the cell and spreads further to repeat
    ii. Epidemiology:
        - Occurrence:
            - A newly recognized pathogen, which we originally assumed was the same as other pneumoniae
            - No localization: Worldwide
            - Serosurveys – increases with age, sharply until adolescence end, then slower until age. Women lower antibodies than men
            - Responsible for 10% of CAP
        - Reservoir: Humans
        - Transmissions: M/L Droplets? Nasal Secretions, P2P?
        - Communicability: Not known
        - Temporal Pattern: Not known
    iii. Pathogenesis: not much known other than life cycle. Uses Type 3 secretion apparatus.
    iv. Clinical:
        - Largely asymptomatic, most people are just carriers
        - Pneumoniae – common in elderly, 10% of all CAP
        - Pharyngitis/Bronchitis

v. Diagnosis:
    - Stains (Giemsa, or antibody)
    - Serology (MIF recommended, or ELISA)
    - Tissue Culture (with cells)
    - Antigen Detection
vi. Treatment
    - Not beta lactams (But why?)
    - Macrolide/Tetracyclines (good for soft tissue infections, apparently)
vii. Prevention
    - Unknown, but immunity sucks

2. *Chlamydophila psittaci*
    a. For your consideration:
        i. Why has the incidence of C. psitaci been declining in the US?
            - Tetracycline poultry feed.
            - All imported birds quarantined 30 days and treated.
            - Increase in domestic bird industry.
        ii. How is C. Psittaci prevented?
            - Tetracycline in feed and quarantine.
    b. Review questions
        i. What is the reservoir of C. psittaci?
            - Birds, esp. of psittacine nature, + mynah dove pidgeon
        ii. Who is mostly likely to be infected by C. psittaci?
            - Bird owners, those who work with birds, including poultry farms, vets, pet store workers.
        iii. Why has the incidence been declining in the US?
            - Good prevention strategies have been implemented – tetracycline in feed, quarantine by 30 days, and less reliance on foreign bird industries.
        iv. What cells are primarily infected by *C. psittaci*?
            - Macrophages, starting with aveolar macrophages and disseminating from there.
        v. What is the mode of transmission of *C. psittaci*?
            - No P2P, but aerosolized poop from bird to human or bird to bird
    c. Swartzburg Framework
        i. Etiology
            - Comes from the Greek word for parrots, same genus as C. pneumoniae
            - More generally, Ornithosis covers all birds
            - 10 genotypes, with different virulences and host preference
        ii. Epidemiology
            - Occurrence: Worldwide
            - Risky popn: Bird owners, people who work in poultry farms, pet store workers, vets.
            - Many outbreaks have occurred typically due to pet stores
            - Decline in US has occurred to good use of prevention strategies

- Reservoir: Psittacine birds, mynah, doves, pigeons.
- Transmission: Bird to human
- Temporal Pattern: None
- Communicability: No P2P

iii. Pathogenesis
- Humans inhale aerosolized organisms from bird feces
- It then infects aveolar macrophages, and can either get destroyed alongside the macrophage, or survive and disseminate to other organs

iv. Clinical
- Commonly asymptomatic
- Pneumoniae due to systemic infection.
- Rashes, fevers, dry coughs, etc.

v. Diagnosis
- Past history very common – 50% report contact with bird
- Serology: IFA, or C' Fixation (less sensitive)
- Chest X-ray
- Culture NOT RECOMMENDED due to virulence

vi. Treatment
- Tetracycline

vii. Prevention
- Tetracyline, in feed, quarantine, not using foreign birds?

3. *Mycoplasma pneumoniae*
   a. For your consideration:
      i. What human diseases are associated with M. pneumoniae in general?
         - UTI, pneumonia
      ii. How does the structure of M. Pneumoniae explain some of the clinical manifestations?
         - The lack of a cell wall causes the immune system learns to recognize proteins on the membrane directly.
         - This crossreacts with other cells across the body, causing target leisions everywhere.
      iii. What are typical settings for outbreaks of M. Pneumoniae?
         - Anywhere with crowding – Prisons, Barracks, Dorms.
   b. Review Questions:
      i. What makes mycoplasma unique among bacteria?
         - It has no cell wall! Unique among human pathogens
      ii. How would you treat someone infected with mycoplasma pneumoniae?
         - Tetracyclines, Macrolides, Fluoroquinolones.
      iii. What are examples of sequela associated infection of M. pneumoniae? What is the mechanism for development of these conditions?
         - Some sequelae include Stevens-Johnsons syndrome (severe skin reactions) and Raynaud's phenomenon (arteries literally just stop sending blood) well as ALL the -itises.

- The lack of a cell wall causes the immune system learns to recognize proteins on the membrane directly.
- This crossreacts with other cells across the body, causing target leisions everywhere.

c. Swartzburg Framework
   i. Etiology
      - Mycoplasmas – eubacteria that have reduced genomes from bacterial ancestors. Smallest free living organism
      - No cell wall! Crazy
      - Grows without other cells.
      - M. pneumoniae one of 3 major human disease causing ones (M. hominis, Ureaplasma Urealyticium being the others). Main one to be linked directly to a pulmonary disease
      - Species vary in distribution across US vs China – drug suscpetiblity is higher in US.
   ii. Epidemiology
      - Occurrence: 1% people infected annually, forms 15-20% of all CAP.
        - Risk pop'n: Young people, peaking in adolescence, smokers
        - Outbreaks common in crowded areas with young'ns, families.
        - Worldwide, decreasing, but epidemics every 4.5 years ish
      - Transmission:
        - P2P via M/L droplets, respiratory secretions. Fomites, possibly?
      - Temporal: none, except for recurring epidemics
      - Reservoir: Humans
      - Communicability: 1-4 Weeks of incubation
   iii. Pathogenesis
      - Penetrates the mucociliary blanket with its motility
      - Attatches with terminal organelles
      - Causes ciliostasis (literally, cilia stop moving)
      - Causes the death of other individual cells with Hemolysin
      - It itself generates a crazy amount of hydrogen peroxide to damage other cells
      - Also has interplay with immune system, activating it through these relationships
        - Mitogen for T and B cells.
        - Increases interferon production.
        - Decreases CMI to unrelated antigens.
        - Immune complexes.
        - Autoantibody (lymphocytes, lung, heart, kidney, brain, smooth muscle).
          i. IgM antibodies to the I antigen on erythrocyte membranes
   iv. Clinical
      - Tracheobronchitis primarily
      - Asymptomatic

- Pneumonia
- URIs in general
- Other stuff extrapulmonarily e.g. Steven-Johnson's and Renauds sysndrome

v. Diagnosis
- All kinda iffy
- Isolation – super slow, inconsistent
- Complement fixation – lacks specificity and sensitivity
- Commercial serologic tests - Lacks the above, and also relies on patient compliance
- PCR is pretty good but not widely available, and also has issues in cases of unknown eitiology.

vi. Treatment
- Tetracyclines
- Macrolides
- Fluoroquinolones
- Resistance is developing to the latter two

vii. Prevention
- No idea rn, immunity is also weak

4. *Legionella pneumophila*
   a. For your consideration
      i. What is the habitat for Legionella SPP?
         - It lives in freshwater, specifically with amoebae, (cause it requires L-cysteine)
      ii. What is the difference between legionellosis and Pontiac Fever?
         - Legionellosis – hours-days (2-14) of initial headache, then fever, then major coughs and pains, into systemic issues. Big issues with systemic symptoms, only 50% of cases actually have pneumonia, 5-30% fatality
         - Pontiac fever – Flu-like fever, very minor, but most people who are expode get it, but never lethal as far as we know.
      iii. Why do outbreaks occur?
         - Water storage that is improperly treated. Typically we're looking at poor chlorination and heating, etc.
      iv. How can we prevent outbreaks?
         - Do better chlorination! Typically we're looking at poor chlorination and heating, etc.
   b. Review Questions
      i. Describe three strategies that intracellular pathogens use to survive and give an example of a pathogen for each mechanism. What strategy does legionella employ?
         - Survival in a phagolysosome (like leishmania)
         - Escape from the phagosome (like shigella)
         - Growth in a specialized endosome (this is what legionella uses)
      ii. What are the two clinical symptoms associated with legionella?
         - Legionellosis and Pontiac Fever

iii. What special factors does legionella require for growth?
    - Needs L-cysteine
iv. What are the risk factors for infection?
    - Staying in other buildings, recent repairs on water, swimmers, hotels
    - Diabetes, hepatic failure, smoking,
    - Age, older males
    - Hospital settings.
v. Give what you know about its reservoir, how would you go about preventing legionella?
    - Higher levels of chlorination
    - Better heating

c. Swartzburg Framework
    i. Eitiology:
        - Legionella spp. In general can cause diseases, but most important one is L. pneumophilia serogroup 1.
        - It grows in a specialize endosome, preventing phagosome fusion, and requires amino acids (specifically L-cysteine).
        - Virulence factors:
            - Has endotoxins (LPS) and proteases.
    ii. Epidemiology:
        - Occurrence: Most cases are sporadic, causes 10-15% of CAP
            - Notable risk factors occur with nosocomial environments, where older people are at risk of infection and death
            - E.g. Flint – change in water lowered chlorine levels and increased legionella infections markedly (2014-2015
        - Reservoir: Warm water first (25-40 C), possibly zoonotic
            - Natural reservoir – rivers, lakes, etc.
            - Artificial reservoir – municipal reservoirs, air condition, cooling otwers, etc. etc.
        - Transmission: Aerosols accepted theory, but also aspiration of potable water
        - Temporal: Likely summer/fall – but occurs year round.
        - Communicability – none.
    iii. Pathogenesis:
        - Inspiration, macrophage phagocytosis
            - Pneumonia + dissemination
    iv. Clinical:
        - Legionella is implicated in both legionellosis and Pontiac fever.

	Legionnaires' disease	Pontiac fever
Clinical features	Pneumonia: cough, fever, chest pain	Flu-like illness (fever, chills, malaise) without pneumonia
Radiographic pneumonia	Yes	No
Incubation period	2-14 days after exposure	24-48 hours after exposure
Etiologic agent	*Legionella* species	*Legionella* species
Attack rate*	< 5%	> 90%
Isolation of organism	Possible	Virtually never
Outcome	Hospitalization common Case-fatality rate: 5-30%**	Hospitalization uncommon Case-fatality rate: 0%
* Percent of persons who, when exposed to the source of an outbreak, become ill. ** Percent of persons who die from Legionnaires' disease or Pontiac fever.		

-

v. Diagnosis
    - Culture, Urine antigen, serology, DFA stain
        - Decreases in sensitivity and specificity in order
vi. Treatment
    - Antibiotics and early diagnosis
vii. Prevention
    - Turn on the shower!
    - Use sterile water for nebulization
    - Chloramination (chlorine + ammonia)
    - Super heating
    - UV light
    - Copper silver ionization system etc.
    - Hospitals need it.

5. Respiratory anaerobic disease?

a. For your consideration:
    i. What is the habitat of human anaerobes?
        - They live where no oxygen exists: colons, under your gums
    ii. What is the difference between obligate, facultative and microaerophilic anaerobes?
        - Obligate – absolutely needs to be without oxygen – produces toxic metabolites (superoxides, peroxides)
        - Facultative anaerobes – they can survive in oxygen and lackthere of, going to be more efficient with oxygen
        - Microaerophiles – they live best with a little oxygen, but not standard atmospheric
        - Aerotolerant organisms – it don't matter – they live everywhere
    iii. Name four species of *Clostridium* that cause human disease
        - Tetani (tetanus)
        - Botulinum (botulism)
        - Perfringens (gas gangrene, food poisoning)

- Difficile (colitis)

iv. What is aspiration pneumonia? How does it occur? What are its consequences?
- Aspiration pneumonia occurs from matter inhaled from the mouth/stomach, occurs due to infections from the oropharangeal areas (gums, etc., and a compromised respiratory tract). It can really eat through the lung and drain out.

b. Review Questions
i. How does oxygen kill? What mechanisms do facultative anaerobes use to survive in environment with oxygen?
- Through metabolic processes, forms reactive oxygen species within the organism that kills it. Facultative anaerobes has various detoxifying pathwasy that processes these (e.g. peroxidases)

ii. Which is more efficient at producing energy: Aerobic or anaerobic metabolism? How many ATPs are produced for each? 38 to 2 for aerobic to anaerobic.

iii. What are some of the clinical clues for anaerobic infections?
- Location, abscess formation, infection near mucosal areas,

c. Swartzburg Framework
i. Eitiology
- Big thing – distinguish between obligate, facultative, and microaerophilic anaerobes.
- Commonplace within our body for Gingival crevices and colon.
- Clinically important ones – Fusobacterium, Peptococcus/Peptostreptococcus, Bacteroids fragilis, clostridium, etc.
- Habitat for Clostridium – soil/Intestine of man and animals

ii. Epidemiology
- For Pneumonia – 5-15% of cases are Aspiration pneumonia
  - Common in nursing homes and drug overdosers
  - Often associated with anesthesia and alcohol use

iii. Pathogenesis
- Basically when the normal flora gob beyond the mucus membrane – e.g. nail, etc., It also needs to be a reduced oxygen concentration (e.g. nail into foot, then sealing)
- Most things are complex – often synergistic in that multiple species are involved in an infection
- For aspiration pneumonia – typically aspiration of oropharyngeal content into the lung area and production of toxins.

iv. Clinical
- Just itises of any place basically – gingivitis, sinusitis, chronic otitis, peritonitis

v. Diagnosis:
- Clues for diagnosis is typically location, gases, odorus, and evidence of necrosis.

vi. Treatment:
- Antibiotics, drainage, hyperbaric oxygen

vii. Prevention:
- prevent aspiration in risk populations, dental hygiene

6. Fungal respiratory pathogens

a. For your Consideration:

i. Be able to defin and give examples of: yeast, mold, mycelium, hyphae, pseudohyphae, dimorphic fungi, saprobe
- Yeast and Mold below:
- Mycelium – many hyphae together
- Hyphae – tubular, multicellular structures that form molds, can be septate or aseptate (separated vs not)
- Dimorphic fungi – fungi that can be both molds and yeasts depending on environment (typically temperature)
- E.g. Fungi can be molds in vitro 25 C, free living, and then become parasitic yeasts in the body.

ii. Why are fungal infections in humans increasing?

b. REVIEW QUESTIONS

- What is a mold? Yeast?
  - Mold – multicellular, form in hyphae (tubular, filamentous structures), and reproduce both asexually and sexually via spores, typically.
  - Yeast – unicellular fungus that reproduce via budding – sometimes form "pseudohyphae", which look like hyphae but aren't.
- How do fungi differ from bacteria?
  - They're eukaryotic, and have chitin in their cell wall
- Name two opportunistic fungal pathogens associated with HIV.
  - Candida spp. Especially Candida auris
  - Aspergillus
- Why is the incidence of fungal infections increasing?
  - Due to population growth into areas with environmental pathogenic fungi
  - More compromised hosts due4 to medical procedures, chemotherapy, etc. Coccidiodomycosis

c. For Your consideration

- What type of organism is C. immitis?
  - Dimorphic fungus – free living as mold, parasitic form yeast in body
- Where does C. immitis typically occur?
  - The disease typically occurs in the California Valley
- What ist he infectious form of this fungus?
  - The infectious form of this fungus is mold
- What is the natural history of infection?
- Who is at risk for serious disease?

d. Review questions

i. Can person-to-person transmission of coccidiodes immitis occur? Why/why not?
- No – the infectious form is the mold, but we only have the parasitic yeast form in our body.

ii. What condition increase transmission of coccidiodes immitis?
    - Dry conditions make the mycelia extremely fragile, such that they can be dispersed in the air and remain there.
iii. What are the risk factors for candidiasis?
    -

e. Swartzburg Framework
    i. Etiology
        - Coccidiodes is a dimorphic fungi, has two species (immitis and posadasii) that we care about.
        - They grow as mold a few inches below the surface of desert soil
        - Has two phases: the saprobic, free-living phase and the parasitic phase:
            - The mycelia in the free living form and break up into arthroconidia which can then be inhaled
            - The arthroconidia are inhaled and become parasitic yeasts, where they form spherules that self maintain and also emerge out as endospores
            - Those endospores in the environment form back into mycelia.
    ii. Epidemiology
        - Immitis occurs in California, Arizona, Texas, as well as everything south of it.
        - All largely the same climate/soil – sharp upsurges occur when soil is disturbed (e.g. building, dust storms)
            - Dry periods after a rainy season extra bad
        - Valley fever in the valley is common (whoa).
        - A recent uptake has occurred due to movement into endemic areas.
        - Risk populations – Those with diabetes, those in prisons in endemic areas
    iii. Pathogenesis:
        - Immitis infection activates the immune system – however, macrophages and neutrophils can't really take care of the large structures of fungus
        - T lymphocytes can actually respond, and cause inflammation.
            - Thus, immunocompromised patients, infants, and non-whites are susceptible. To infection
    iv. Clinical
        - Basically asymptomatic in 60% of cases
        - Typcially fever, fatigue, and general pains and coughs
        - Complications can occur – residual lung nodules, cavitations, and extrapulmonary infection
        - Chronic complications can occur for diabetics and immunocompromised people, disseminating to the bone, joints, meninges.
    v. Diagnosis:
        - Serology (EIA, LA, etc.
        - Histopathology
        - Skin test
    vi. Treatment
        - Antibiotics (like amphotericin)

vii. Prevention
- A Vaccine is in development, but not quite there.

7. Sexually Transmited Infections
   a. Have a sense of the most important STIs and the diseases they can cause
      i. Most important – Syphyllis, Herpes, and Chancroid
   b. How has the epidemiology of chlamydia, gonorrhea, and syphilis changed in the US in the last 20 years?
      i. While Gonorrhea and syphilis have gone down or remained stable, chlamydia has risen crazily. (moreover, Drug resistance gonnorhea is around now, not great)
      ii. We've observed increases in all three in the last 5 years
   c. How do we use screening to prevent STI's?
      i. We screen risky populations to make sure statuses are known – to make sure that people know
   d. What tools beside screening are effective in preventing STI's?
      i. Behavioural – Monogamy, reducing partners
      ii. Barriers (Specifically, condoms)
      iii. Vaccines for those that have it (HPV and HBV)
8.

Dr. RILEY'S SECTION

1. MERS
   a. What are the risk factors for MERS infection?
      i. Male, older age, and underlying medical conditions
   b. Compare and contrast SARS and MERS
      i.

	SARS	MERS
Occurrence	Worlwide	Middle East
Reservoir	Bats?	Camel
Transmission	Airborne/P2P	Airborn, less P2P
Risk factors	HCW, Nebulizers	Male, Older Age, Medical conditions
Timelines	4-6 days, death in 24 days.	5 days-2 wks, death in 11.5 days
Symptoms	Fevers, chills, diarrhea, progression to pneumoni and ARDS	Fevers, coughs, chills, etc., rapid progression to pneumonia and ARDS, and septic shock.
Susceptibility	Not in primates but in hamsters/mice	Marmosets and rhesus monkeys susceptible

2. PERTUSSIS

a. Learning Objectives
    i. Describe the main clinical features of pertussis
        - Most notable feature is the “whopping cough”, where large amounts of mucous cause a sort of wheezing in infants.
        - Largely in infants, though adolescents and adults can contract an infection (without symptoms)
    ii. Describe the changing epidemiology of pertussis in US and CA
        - We are seeing increasing incidence especially at >10 years of age, where the Tdap booster is needed but not often administered.
        - There is large incidence in white and Asian/pacific islanders.
    iii. Name the two types of vaccines against pertussis and give the reason for the need for a new pertussis vaccine
        - Whole cell, acellular (wP, aP), which are dangerous + not effective enough in preventing infection + transmission.
        - Current vaccines wane after 10 years – while some memory may exist, it’s not sufficeint
    iv. Describe the new recommendation for pertussis vaccine.
        - DTaP 5 immunizations between birth and 4-6 years.
        - Tdap once at 19-21.
        - Routine use at 11-12 years of age, with special focus for adults dealing with young infants
        - No defined minimal interval
b. Review Questions
    i. Why is the incidence of pertussis increasing?
        - Waning protective immunity from vaccines
        - Infants and adolescents surving as reservoirs
        - Increased reporting
        - Vaccine exemptions
        - Poor herd immunity (especially wP vs aP)
    ii. What is the correlate of protection?
        - Anti-PT antibodies, (Pubmed mentions pertactin and fimbral hemagglutinins as well)
    iii. Compare and contrast the whole cell inactivate vs. acellular vaccine.
        - Whole cell inactivated cells had arount 300-500 different proteins. Very inefficient,a nd had sever side effects in some children. Huge variability in vaccine due to strain variability
        - Acellular relies on PT, FHA, and PRN, as well as two different fimbrial proteisn. Which is more efficient, but it’s been shown that a higher level of vaccination is needed for proper immunity, and that it might not prevent being communicable
    iv. What are the virulence factors in Bordatella pertussis?
        - Pertussis Toxin (PT)
        - Tracheal Cytotoxin (TCT)
        - Adenylate cyclase toxin (ACT) – same as e coli

- Heat labile toxin – not same as e coli
- LPS
- FHA and PRN are receptor binding factors
- Fimbriae

c. Swartzburg
   i. Etiology
      - *Bordatella pertussis* – small gram-negative bacterium
   ii. Epidemiology
      - Occurrence – worldwide, 10 mill new cases per nanum, deaths largely in pertussis
      - Increasing incidence for less than 5 and over 10, due to waning incidence, especially in whites and Asian/pacific islanders
      - Transmission: typically infectious during the asymptomatic period and up to 2 spasmodic clothes, and can remain up to 6 weeks.
         a. Can be transmitted through adults/adolescents
   iii. Pathogenesis
      - Pertussis Toxin and ACT both upregulate cyclic AMP, which messes up initial signaling
      - TCT destroys ciliated cells
      - Fimbrae and FHA, and PRn used to attatch.
   iv. Clinicial
      - The so called whooping cough
      - 3 weeks of incubation, 2 weeks of mucus, then 6 weeks of coughing
      - Communicable once the symptoms are evident
   v. Diagnosis
      - Culture not sensitive but specific
      - PCR sensitive and specific
      - DFNA very insensitivie, still specific
      - Lab criteria combine the top two
   vi. Treatment
      - Supportive care
      - Antibiotics to suppress transmission.
   vii. Prevention
      - Pw had issues with side effects, discontinued in the 1990s
      - Pa introduced int eh late 1990s.
      - Duration of protection (4-14, 5-6 years respectively), at least 2 doeses for protection.

3. RSV
   a. Review Questions
      i. What are the risk factors for severe disease?
         - Elevated levels of IgE histamine anti RSV
         - Age (< 6 months, > 65 yrs)
         - Immune Deficiency
         - Heart disease

- Chronic lung disease

ii. What is the correlate of protection
- IgG antibody, Maternal antibody.

b. Swartzberg Framework

i. Etiology
- RNA, negative single stranded virus
- 10 protiens, F(usion) and G(attatchment) protiens are the most important, and are important for the life cycle
  a. Specifically, G allows it to attatch, F protein incorporates the membranes together, and injects the RNA properly.
- Two groups – A and B

ii. Epidemiology
- Occurrence – world wide
- Reservoir – humans
- Temporal – late fall, winter, early spring
- Most common cause of RTi in infants/children
- Also problematic in adults > 65
- Risk factors – age: < 6 months, congenital heart disease, chronic lung disease, immune difficiency, crowded places (e.g. day-care centers)
- Transmission: Respiratory secretions/fomites. Shedding is up to 4 weeks, allowing for outbreaks.

iii. Pathogenesis:
- RSV can block anti-viral response, but activates TLR4. Necrosis and destruction of ciliated epithelial cells are done thoruhg inflammation.
- Pneumonia will occur if these processes go to the aveolar spaces.
- Can cause cellf using (the S of RSV is syncytial)

iv. Clinical Spectrum
- Incubation of 4-5 days
- Discharge of mucus (rhinorrhea), coughin, wheezing
- Cmplications – Otitis media, bronchioloitis, pneumonia, apnea.

v. Diagnosis
- Clinical symptoms
- Elisa
- RT-PCR
- Viral isolation

vi. Treatment
- Antivirals (just not globulin cause htat expensive)
- Need to be used early.

vii. Prevention
- Detergent inactivates the virus, so that's cool
- Handwashing
- Avoided crowded places
- Passive prophylaxis for high risk infants
- Vaccine in development.

4. HIV
    a. Learning Objectives
        i. Describe the HIV classification scheme
            - HIV -1 MONP, M is subdivided based on envelope gene sequence
            - HIV 2, based on the 7 clades.
        ii. Describe 3 highlights of the current epidemiological situation of AIDS/HIV infection in the world, and 3 highlights for the US
            - World:
                a. Still large amounts of cases (36.9 million in 2017).
                b. Less deaths per year, but increases in middle east/north Africa, and eastern Europe.
                c. Increasing amounts of case, influenced by previous status
            - US:
                a. In general, decreasing. More cases amongst young'ns – complacency? Drug use?
                b. MSM dominates male cases, heterosexual contact for females
                c. African americans (both) and white males dominant cases. Increasing amounts in Asians
        iii. Describe 4 factors that influence progression of HIV infection to AIDS
            - Host factors age, genetic factors
            - Increased viral load
            - Concurrent STD
            - Infection with multiple strains
        iv. Describe the current case definition of AIDS
            - HIV infected persons with Tcell count of less than 200/uL
            - CD4+ T lymphocyte percentage of total, less than 14%
        v. Describe the 3 main stages of HIV progression to AIDS
        vi. Be able to name the major opportunistic diseases of AIDS
            - 3 additional clinical conditions (Pulmonary TB, recurrent pneumonia, cervical carcinoma)
        vii. Name one screening test and one confirmatory test used to diagnose HIV infection
            - Screening – EIA
            - Confirmatory – Western Bot, IFA, NAAT. Serologic not good for pregnant women or Newborns. They should use viral load detection
        viii. Describe the viral targets of drugs now used to treat AIDS
            - Nucleoside and non-nucleoside – reverse transcriptase inhibitors
            - Protease inhibitors (used for packaging)
            - Integrase inhibitors (use for inhibition)
            - Entry and Fusion inhibitor
        ix. Describe at least 5 components of AIDS prevention
            - AIDS education
            - Promoting condoms
            - Voluntarhy testing

- Prevention and treatment of sexually transmitted infections
- Harm reduction for drug users
- Blood supply
- PrEP – VERY IMPORTANT. Good for materinal-tochild tx, or commercial sex workers.
- Post-exposure prophylaxis – given 2-3 days after exposure, continued for 28 days.

b. Review Questions
   i. Name two proteins found in the viral envelope.
      - Gp41, gp120 (for transmembrane and docking respectively)
   ii. How is the epidemiology of HIV in the US different from that in developing countries?
      - Generall, decreasing, Notable that life expectancy has risen dramatically in Sub-saharan African countries, while slight increases are true in US.
   iii. Describe the life cycle of HIV
      - HIV uses CCR5 or CXCR4 co-recptors (or both) to enter the cell. At that point, reverse transcriptase forms the positive strand of the DNA. This then gets integrated to the main DNA strands and is then produced and packaged from there.
   iv. What was the first country to eliminate vertical transmission of HIV?
   v. What factors affect transmission and progression of disease?
   vi. What part of the virus life cycle is affected by current treatment options?
      - Entry/fusion, reverse transcription, integration, and packaging and budding.
   vii. How is HIV diagnosed?
      - Initial screening is done by EIAs
      - Confirmation is done by various methods, including western blots, NAATs, viral load screning
   viii. What are some of the AIDS defining illnesses?
      - Herpes Zoster, Oral ulceration, tuberculosis, gingivitis.

c. Swartzburg Framework
   i. Eitiology:
      - An RNA retrovirus, has 2 major surface protein, aq lipid membrane, and RNA +reverse transcriptase
      - Classification Scheme:
        a. HIV-1
           i. Groups M, O, N, P (Major, Outlier, New, and P)
           ii. Group M divided into A-D, F,H, J, K (skip E, G, I), with B being the most important for US.
        b. HIV-2 has 7 clades, largely in West Africa
      - Life Cycle
        a. HIV uses CCR5 or CXCR4 co-recptors (or both) to enter the cell. At that point, reverse transcriptase forms the positive strand of the DNA.

This then gets integrated to the main DNA strands and is then produced and packaged from there.

b. Viral replication is at 10^8 to 10^9 –
    i. Lots of quasispecies created by high replication – 1/10000 mutation/genome/replication cycles.
c. The viral load remains near constant, well over the immune response.

ii. Epidemiology:
- In ’85, was constrained to central africa largely, but by 95’ had spread massively
- 36.7 million in the world increases of 1.8 million new cases per year with 1 million deaths.
- World:
  a. Still large amounts of cases (36.9 million in 2017).
  b. Less deaths per year, but increases in middle east/north Africa, and eastern Europe.
  c. Increasing amounts of case, influenced by previous status
- US:
  a. In general, decreasing. More cases amongst young’ns – complacency? Drug use?
  b. MSM dominates male cases, heterosexual contact for females
  c. African Americans (both) and white males dominant cases. Increasing amounts in Asians

iii. Pathogenesis
- An early infection will go through the regular life cycle like above
- During the primary infection phase, you have a huge 2 million HIV genomes/ml.
- HIV antibodies causes it to decrease and plateau.
- There is a progressive fall in CD4 lymphocytes from a peak of 1000/ml, which Is hwen you start having problems.
- At this point, you will eventually rpgoress to disease.

iv. Clinical:
- We lookf or symptoms of low CD4 T cell coutns in percentage or absolute (> 200/ul or 14%)
- We also look for other conditions – Pulmonary TB, recurrent pneumonia, cervical carcinoma, candidiasis, Cryptococococssis, histoplasmosis, PCP, M. TB, M. MTM. Herpes Zoster, Herpes simplex HPV. Cryptosporidiosis.
- Progression:
  a. Asymptomatic infection phase (clinical category A)
      i. Healthy, normal counts – slowly dropping. High viral load Distinguished between A1-A3 T cell count per microlitre
  b. Early symptomatic infection phase (Category B)
      i. CD4+ T cells fall, early opportunistic infections.
  c. Aids defining opportunistic disease then occurs:
      i. PCP, TB, CMV, Herpes, MAC, protozoal infections, etc.

ii. CD4 counts less than 200/ul blood
iii. Same sort of categories as A/B.

- WHO Clinical staging is similar – Stage 1 asymptomatic, Stage 2 is initial stuff, Stage 3 is serious problems, stage 4 is basically everything else oops.

v. Diagnosis
   - Initial screening is all EIA style
   - Confirmation is done with Western blot, IFA, NAAT, for viral load.

vi. Treatment
   - Anti retroviral drugs! Reverse transcriptase inhibitors, Protease inhibitors, fusion inhibitors, entry inhibitors, integrase inhibitors.
   - ART can have issues you NEED tot reat HIV co-infected individuals just in case.

vii. Prevention
   - Many strategies:
     a. Largely his AIDs education and awareness
     b. Behaviour change programs
     c. Promoting condoms
     d. Testing and counseling
     e. Big ones:
        i. PrEP – Helps prevent transmission especially when no agreement is found, e.g. discordant couples. Also, maternal-to-child tx.
        ii. Post-exposure prophylaxis – drugs etc.
     f. Vaccines have started a lot, but failed.