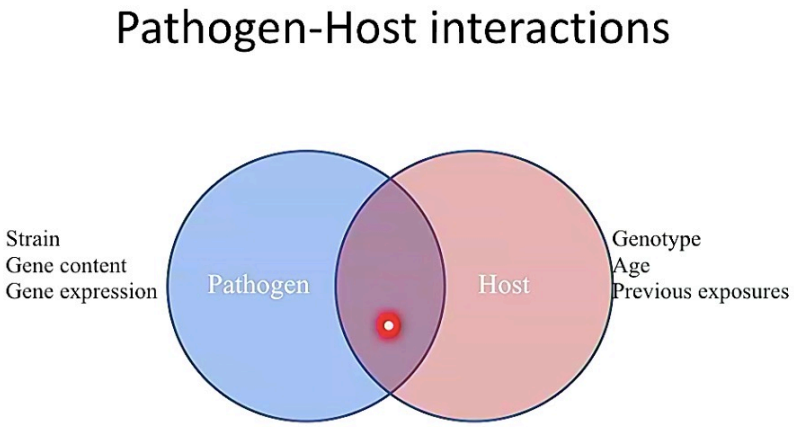
Pathogenesis of Bacterial Infection

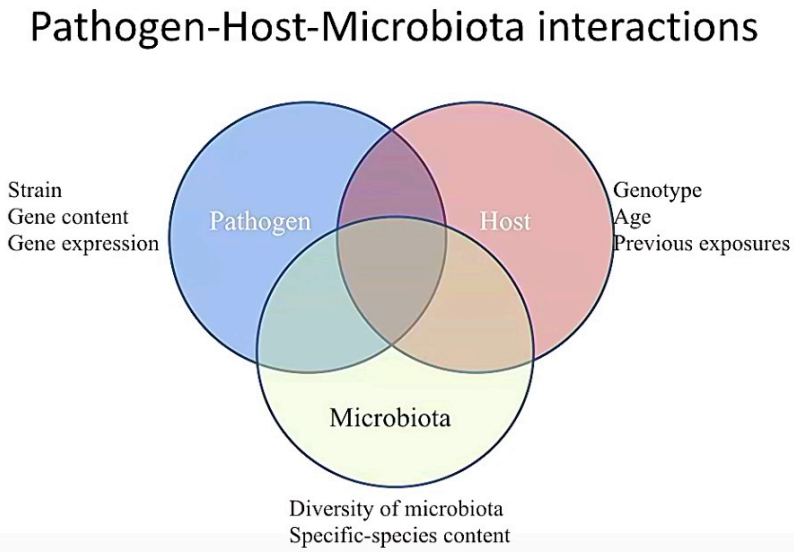
Lecture 1: genetic approaches to studying pathogenesis

pathogens and commensals
- pathogen: organism capable of causing disease
- commensal: (normal flora) able to live in association with another organism without causing damage
- but in reality they exist along continuum from pathogen to commensal

what makes a pathogen?
- must be able to replicate and survive
- can often
  - gain access to, replicate in and persist at usually sterile sites in the body (blood tissues etc)
- colonisation and interact leads to host damage and dysregulation (disease)

infectious disease
- when there is level of damage which results in perturbation of homeostasis
  - this damage is determined by interaction of pathogen with host
- variability of disease depends on
  - particular host
  - particular pathogen
  - host microbiota





importance of host immune status
- host genotype affects both innate and adaptive immune responses
  - polymorphism in immune genes
    - MHC, toll-like receptors, cytokine genes
    - all subtly different in how each individual react to infection with differences in the immune genes
- immune response finely tuned between killing and not damaging host
  - limits pathogen replication spread and disease
  - sometimes host damage gives clinical manifestation of disease
    - strep pneumoniae replicates in lung but does not cause necrosis
    - induces inflammatory response that gives clinical symptoms of pneumonococcal pneumonia

importance of microbiota

- critical for some GI infections
  - clostridium difficile infection usually follows antibiotic treatment which clears gut microbiota
- citrobacter rodentium (EPEC model) infections in mice
  - gut microbiota alters infection outcome
  - affects pathogen gene expression
  - plays role in host immune response

citrobacter rodentium infections

- C. rodentium in different mice:
  - HeJ mice get lethal infection
  - NIH mice no mortality
- HEJ AND NIH mice have different gut microbiota profiles
- microbiota transplant changes susceptibility

what are virulence factors

- factors that bacteria it expresses that allow it to cause damage in host
- factor is the gene product (protein polysaccharide)
- gene encodes virulence factor

virulence factors

- pathogens are special because:
  - gain access to sterile sites, replicate and persist at these sites causing damage
- virulence factors are those factors that facilitate pathogenesis
  - multiple factors for single pathogen
  - expression of particular factors often dependent on host interaction

true virulence factors

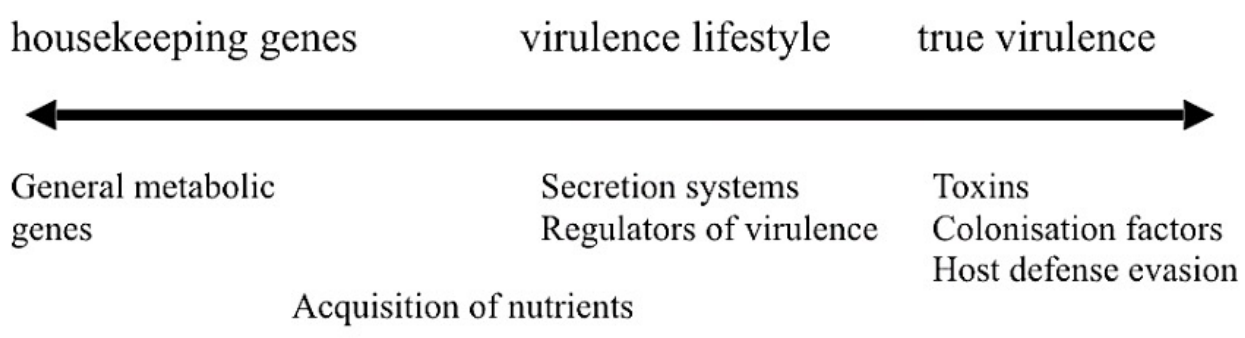
- cause host cell damage
  - toxins (cholera, anthrax, botulinum and tetanus)
- facilitate colonisation (gain access to sterile sites)
  - adhesins, pili, flagella, invasins
- avoidance of immune system (allowing persistence)
  - polysaccharide capsules

accessory virulence factors

- factors involved in acquisition of nutrients at low levels in host
  - proteins for scavenging nutrients such as irons, amino acid and carbs
  - siderophore
- factors for secretion of virulence factors
  - Type III secretion system etc.
  - also secrete non-virulence factors
- factors for regulated expression of virulence factors
  - may also regular non virulence factors

the virulence continuum

- some factors difficult to define
  - e.g. acquisition of nutrients common to pathogens and non pathogens but important to host
  - may be virulence in one host but not other



why study these factors?

- if you're not sure if it's virulence factor:
  - if you have bacteria, knock out the gene you think is virulence factor and bacteria can still grow in lab however cant infect anymore = virulence factor
- expression of these are associated with how cause disease
- learn ways to stop this process happening
  - drug and vaccine targets
- vaccines
  - against virulence factors
  - e.g. toxoid vaccines = diphtheria and tetanus
    - toxoid = activated toxin - still recognised by host but doesn't hurt host
  - e.g. capsule toxin
    - H. influenzae, S. pneumoniae

experimental system

- need systems for studying both:
  - bacteria which causes disease
  - bacteria/host interaction which defines disease
- picking the bacteria
  - where possibly study the organism which causes the disease
  - often highly virulent strains are more difficult to work with
    - precautions to avoid disease
    - often genetic systems less well developed
    - sometimes are difficult to culture
  - may be multiple strains
    - different disease symptoms and severity
- picking disease/host model
  - best to study natural microbe/host interaction
    - not possible for human disease
    - humans = reluctant subjects and are genetically variable
  - find appropriate animal or cell culture model
    - animals genetically defined and cheap
    - may not show same disease as humans
    - may not be affected by same strains

the perfect animal model

- display same disease signs
- similar tissue distribution of bacteria
- acquired by same route as natural disease
- strains more virulent for humans should also be more virulent in animal model
- rare all achieved
  - does model give you useful insights into disease?
- example:
  - S. typhi
    - causes typhoid fever in humans, avirulent in mice
  - S. typhimurium
    - causes mild non systemic disease in humans, but typhoid like disease in mice

differences in disease syndrome

- use of similar but not identical systems:
  - advantages: you will learn about similar disease
  - disadvantages: not same disease
- recent advances in making humanised mice may improve some infection models