MIIM20002 Microbes: Infections & Responses Summary Notes

Lecture 1: Bacterial Pathogenesis

Pathogens: Microorganisms that cause disease
Opportunistic pathogens: are a part of the normal human microbiota however have potential to cause disease in immunocompromised individuals
Normal microbiota (commensals, normal flora): found on the skin (*Staph. Epidermis*) and mucosa - Typically colonise surfaces/niches but don't cause disease - Have a specific and sustainable association with host - Can become pathogenic if found elsewhere in the body - 'train' the immune system for improved efficiency and improved host metabolism - competitively inhibit other bacteria from adhering thus protecting from disease - transient (not present throughout entire lifetime) or permanent

Note: microbes can move between these categories

Mechanism of infection

ASYMPTOMATIC 1. Colonisation via adhesion using fimbriae 2. Penetration through epithelium or between epithelium (some bacteria cause damage without penetration) 3. Replication (while evading the immune system)
SYMPTOMATIC 4. Host tissue damage (release of toxins) 5. Disease (compromise of normal bodily function) 6. Dissemination (other tissues or other hosts) 7. Immunity/Permanent damage, death

Lecture 4 – The Microbiology of Gastrointestinal Disease

Gastrointestinal Disease

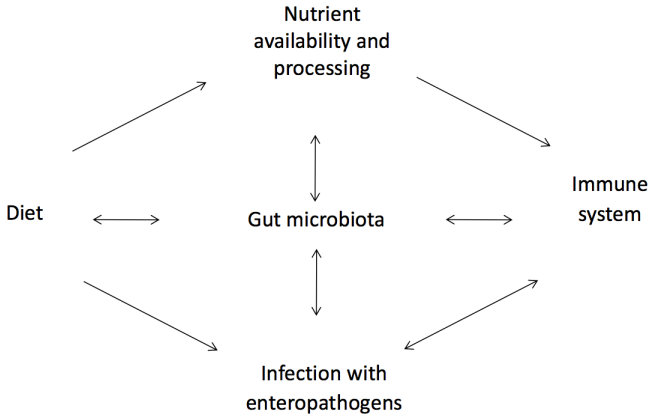
- Involves an array of microorganisms (bacteria, viruses, protozoa (parasites)) collectively known as 'enteric pathogens'
- Cause gastroenteritis (GE) defined as inflammation of stomach/intestines caused by infection or intoxication (presence of microbial toxin) resulting in diarrhoea (principal symptom), vomiting, fever, abdominal pain
- **Diarrhoea** is the abnormal faecal discharge with frequent and/or fluid 'stools'; may contain mucus, pus, blood and/or excess fat depending on the microorganism present; results in forcible expulsion of pathogen aiding dissemination (spread)
- **Dysentry** is bloody diarrhoea resulting from inflammatory disorder of GIT with symptoms including bloody stools, pus in faeces, pain, fever and abdominal cramps

	Bacteria Species	**Virus Species**	**Parasites**
Intoxication	*Staphylococcus aureus, Bacillus cereus, Clostridium perfringens*		
Infection	*Campylobacter jejuni, Salmonella spp., Shigella spp., E.coli* (containing virulence factors), *Yersinia enterocolitica*, *Vibrio cholerae, Vibrio parahaemolyticus*	*Rotavirus, Calcivirus (Norovirus), Adenovirus*	*Giardia lamblia, Cryptosporidium spp., Entamoeba histolytica*

Reservoir of infection: any person, animal, plant, soil or substance in which an infectious agent normally lives and multiplies; can harbour agent without harm to self; infectious agents depend on reservoirs for survival

	junctions, allowing *Shigella* to bypass into basal side. From here, *Shigella* can invade enterocytes and is taken up in a phagolysosome. The microbe then lyses phagolysosome using Ipa proteins and replicated in the safetly of cell cytoplasm. Here, IcsA protein is made to induce actin polymerisation, propelling bacteria (using actin tails) into neighbouring cells. Bacteria replication kills enterocytes leading to ulcer formation, bloody/pus filled diarrhoea - *Shigella dysenteriae* produces shiga toxin (Stx), and destroys endothelial cells - Disease is considered self-limiting; administration of antibiotics only under severe conditions - **Laboratory Identification: LNF**, biochemical tests (serotyping, lack of H_2S production, non-motile)
Salmonella spp.	- Invasive pathogen; also an LNF - Most human pathogens grouped in *Salmonella enterica* subspecies *enterica* with over 2400 serovars (type O & H) - Only serovar *Typhimurium* and *Enteritidis* cause human GE - Produce an **acid labile (LT)** toxin and thus need a high ID - Can invade M-cells as well as enterocytes using **salmonella invasion proteins (Sips;** encoded on pathogenicity islands) which induce cellular mediators and mobilise intracellular Ca^{2+} - Induce membrane ruffling leading to uptake of bacteria into membrane-bound vesicles - A **pathogenicity island** is a large area of bacterial chromosome dedicated to virulence encoding many virulence genes such as **adhesins, toxins, invasins** etc. - PIs have different GC content and are large (>30kb); can be transferred horizontally between bacteria - **Virulence Factors:** Two type of *Salmonella* PIs: **SPI-1** & **SPI-2**: SPI-1 is 46kb and encodes T3SS (in particular *Salmonella* invasion proteins) to induce membrane ruffling;

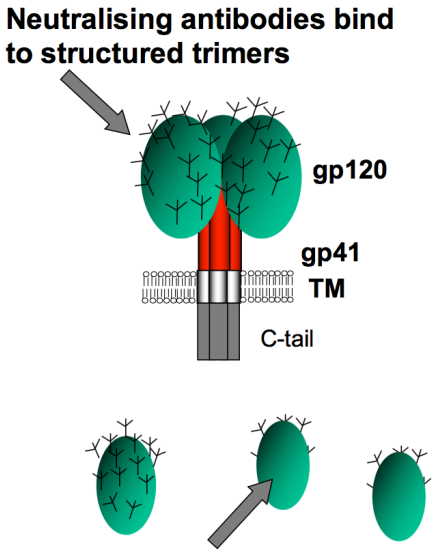
- Treatment for these individuals include faecal transplants; this allows transfer of healthy, diverse microbiota from one individual to another
- However, another method includes growing selected bacteria in a host organism, and transferring these bacteria to an individual with reduced microbiota diversity through a licensed therapeutic (such as a pill)
- Though commensals are largely beneficial for the human immune system, if they escape the GIT, they can cause urinary, respiratory, wound, peritoneal, and blood stream infections; this usually occurs in an abnormal host (e.g. immunocompromised); common organisms include *E.coli* (UTI), *Klebsiella* spp. (wounds, LRTI), *Bacteroides* spp. (wounds)
- **Prebiotics** are dietary supplements that promote beneficial bacterial growth
- **Probiotics** are therapeutic doses of beneficial bacteria, typically *Lactobacillus* spp.; the administration of probiotics may protect an individual from rotavirus (other secretory diarrhoeas), antibiotic associated diarrhoea & development of atopic eczema in babies



Changes in **diet** directly impacts microbiota ratio. This can then lead to changes in the immune system.
As illustrated, changing any aspect has the potential to affect another.

- There are 2 possible roles of commensal microbiota in metabolism and energy maintenance:
  1. They directly provide nutrients from dietary substances (e.g. vitamin K, biotin, folate, CHO from plant sugars, short chain fatty acids from mucins – 10% of calories derived from microbiota metabolism)
  2. Microbiota can alter metabolic machinery of host cells by inducing changes in host genes involved in CHO/lipid metabolism as well as maintaining enterocyte differentiation and function (with short chain fatty acids)

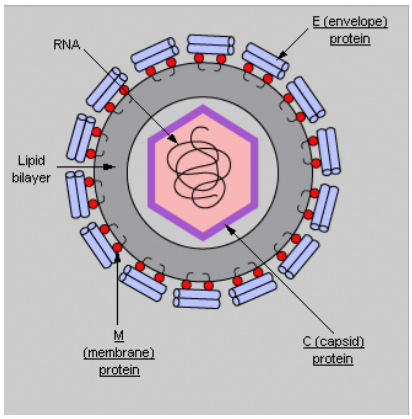
- However, there are unique hurdles for the HIV vaccine:
  - ❖ The natural immune response to HIV does not control the virus, nor protect from 'superinfection' with a different strain
  - ❖ Mechanisms of protective immune response against HIV incompletely understood
  - ❖ Exceptionally high sequence diversity
  - ❖ Ability of HIV to evade neutralising antibody responses
  - ❖ Ability to evade cytotoxic T lymphocyte (CTL) and natural killer (NK) responses
  - ❖ Desire to achieve sterilising immunity
  - ❖ HIV latency and integration (must stop the virus before viral integration into the genome)
- The relative genetic diversity of HIV-1 is significantly more than the genetic diversity of influenza A
- The ideal HIV vaccine:
  - ❖ Is effective in <u>preventing transmission</u> by mucosal and parenteral routes
  - ❖ Safe with minimal risk of adverse reactions
  - ❖ Single dose
  - ❖ Long-lived protection lasting years after vaccination
  - ❖ Low cost, especially in developing countries
  - ❖ Stability and ease of administration with minimal infrastructure
  - ❖ Protect against diverse viral isolates, preventing the need for many isolate-specific vaccines
  - ❖ Therapeutic vaccines to replace therapy & prevent AIDs
- Past vaccines have used the <u>B-cell approach</u> without success; these non-neutralising antibodies bind to decoy glycoproteins which are highly immunogenic – CD4 binding site on HIV must be conserved; this site is protected by the decoy glycoproteins
- The ultimate HIV vaccine may require both cell mediated and antibody mediated immunity
- Broadly neutralising anti-HIV antibodies (bNAbs) were also trialled to combat the disease



Lecture 30 – Epidemic Arboviruses and Wolbachia

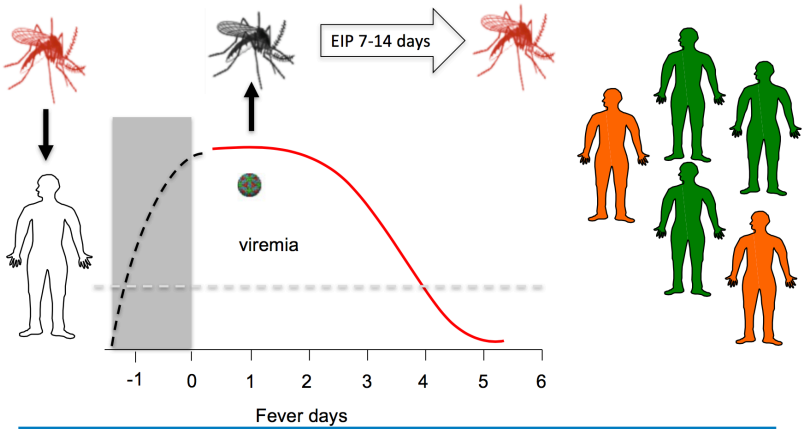
- Medically important *Flavoviruses* include the *Zika* and *Dengue* (Type 1-4) viruses; these viruses are mosquito-borne flavoviruses

Dengue Virus



- *Dengue* virus belongs to a family of *Flavovirus* genus of the *Flaviviridae* family
- Other *flaviviruses* include: Yellow Fever, Japanese Encephalitis and West Nile Virus
- It is an enveloped virus
- 11kb RNA genome
- Three structural proteins (E, C, M)
- **Replication cycle**:
  - ❖ Clathrin mediated endocytosis allows the virus to enter the cell in an endosome
  - ❖ Decrease in pH of the endosome causes the virus to release its ssRNA strand out of the endosome
  - ❖ This viral ssRNA is translated by host ribosomes – produces its own RNA-dependant RNA polymerase to replicate itself in vesicles on the endoplasmic reticulum
  - ❖ Blebs out of the cell through the 'vesicle packets'
- *Flaviviruses* are often quite promiscuous in the cell types they can infect (i.e. can infect mosquito cells and human cells)

Transmission



- The grey area is when an individual is asymptomatic; however, the individual is still infectious to mosquitoes
- At day zero, symptoms start to appear as the viral count in the bloodstream increases – the individual has a viremia and thus, has a very high viral count to infect mosquitoes
- Once a mosquito (*Aedes aegypti*) is infected, it is infected for life