Case 1 - Host Immune Response

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1/27/2018
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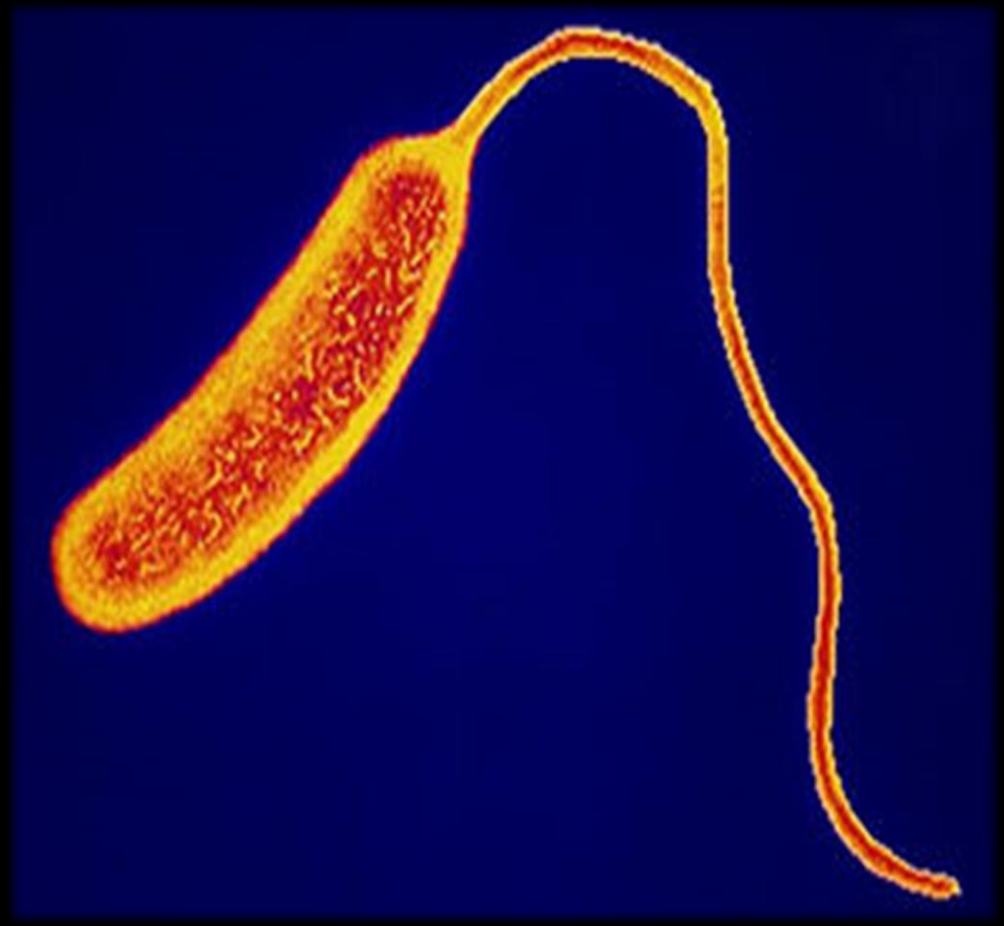
Travelling in India

Fulfilling a long held travel dream, Robert has taken six months off work and is making his way through India taking in the sights, experiencing local festivals and making time to get to know the people. He is cautious in his hygiene, eating and drinking habits but despite this he contracts a diarrhea with voluminous outpouring of fluid accompanied by vomiting. He suspects cholera and with the help of a fellow traveler gets himself to a local hospital where a stool sample is examined and his presumptive diagnosis is confirmed. He stocks up on appropriate fluids and stays put at the hostel he has booked into for a few days, experiencing some minor leg cramping along with the diarrhea. His curiosity about his illness has him reading up on the organisms when he returns to North America and he is left wondering what serotype of Vibrio cholerae he might have contracted, should he have been prescribed antibiotics, was there anything more he could have done to prevent contracting the organism and might he now be a carrier?

Vibrio Cholerae



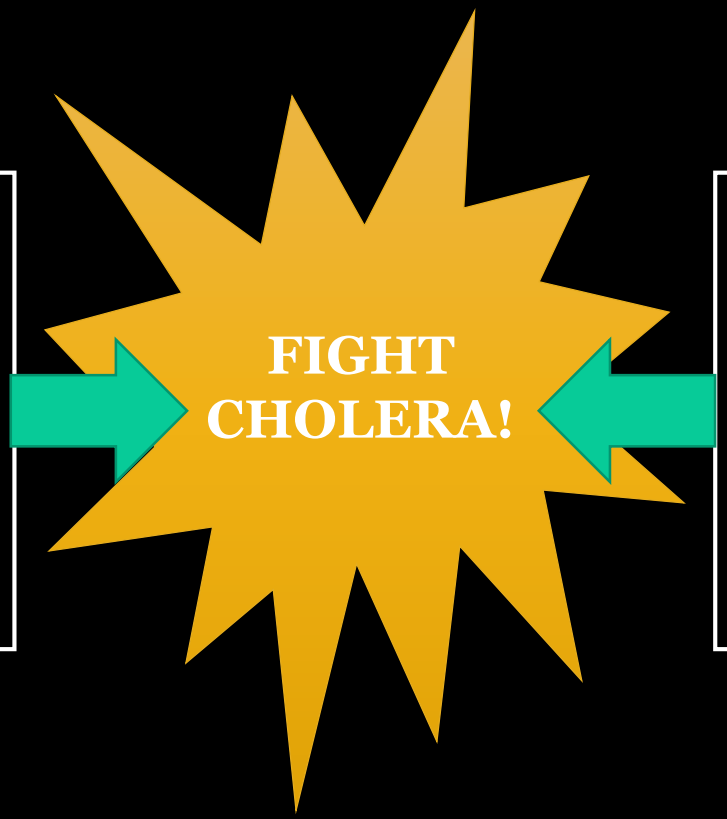
- O1 and O139 serotypes of *V. cholerae* are waterborne pathogens that can cause disease in humans
- Spread via fecal contamination of water or food in areas of poor sanitation and hygiene
- Can reside in host's GI tract and induce significant losses of water and salts, causing vomiting and diarrhea

Question (i)

Host response: What elements of the innate and adaptive (humoral and cellular) immune response are involved in this infection?

Innate Immune Response

- Immediate, nonspecific response
- Body's intrinsic line of defense against *V. cholerae*
- PAMPS + PRRs



Adaptive Immune Response

- Slower response (days) after invasion by pathogen
- Humoral (B cell) and cell-mediated (T cell) immunity

INNATE IMMUNE RESPONSE

- Pathogen-associated molecular patterns (PAMPs) bind to pattern recognition receptors (PRRs) from the host
- This PAMP and PRR binding causes a signaling cascade of various immune responses including:
  - Leukocyte (neutrophil, eosinophil) recruitment
  - Complement cascade activation
  - Phagocytosis of the pathogen
  - Foreign substance removal

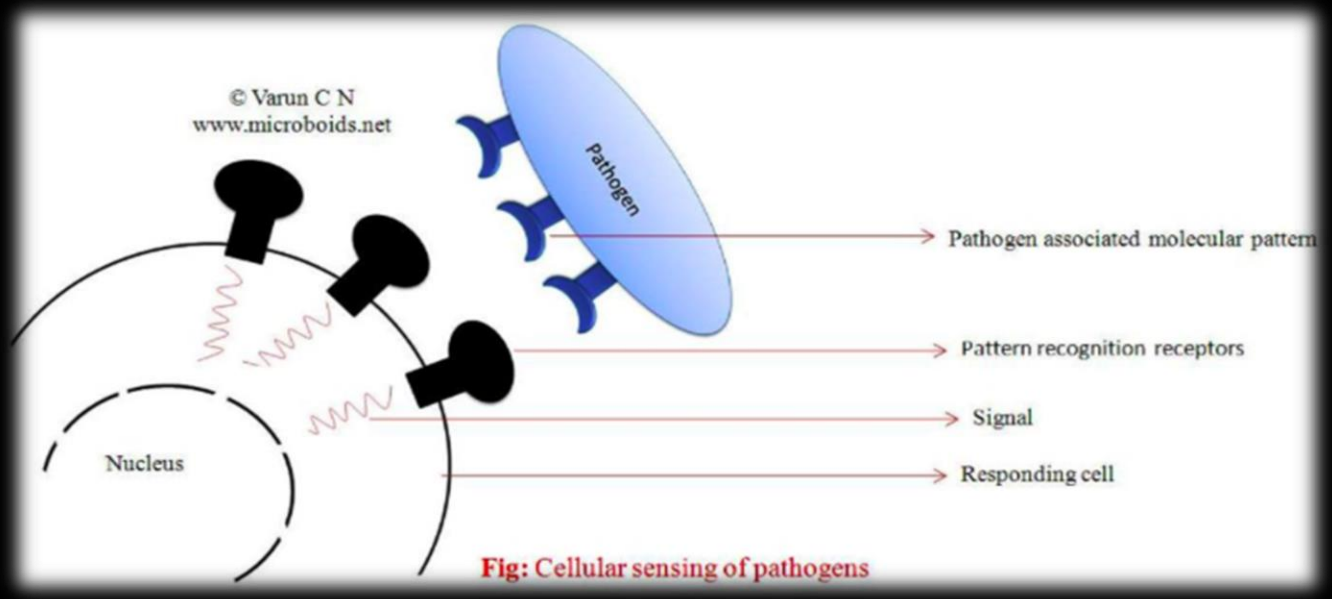
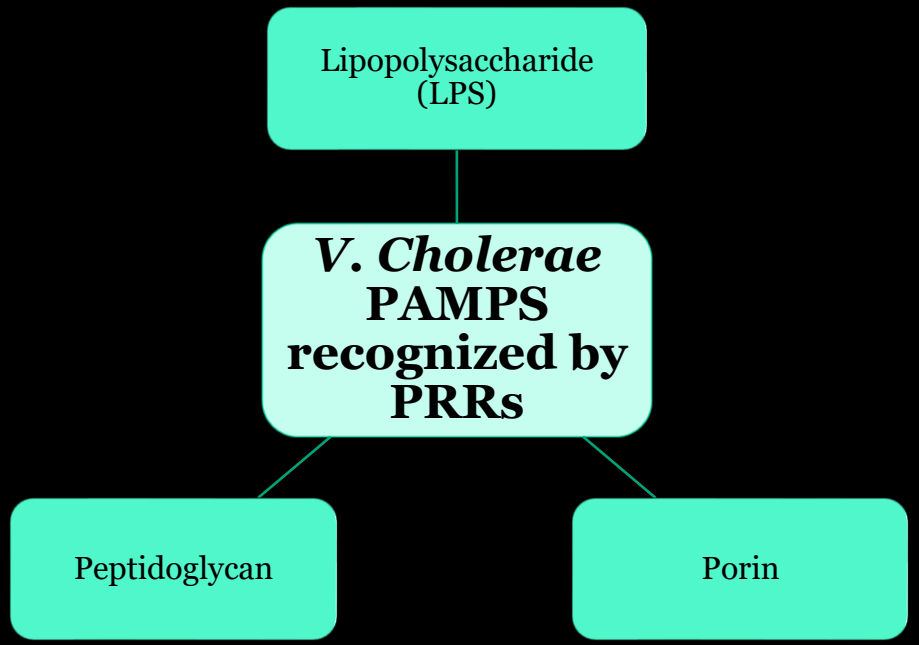


Fig: Cellular sensing of pathogens



INNATE IMMUNE RESPONSE

The body has other intrinsic characteristics that are capable of destroying *V. cholerae*

Gastric acid in stomach

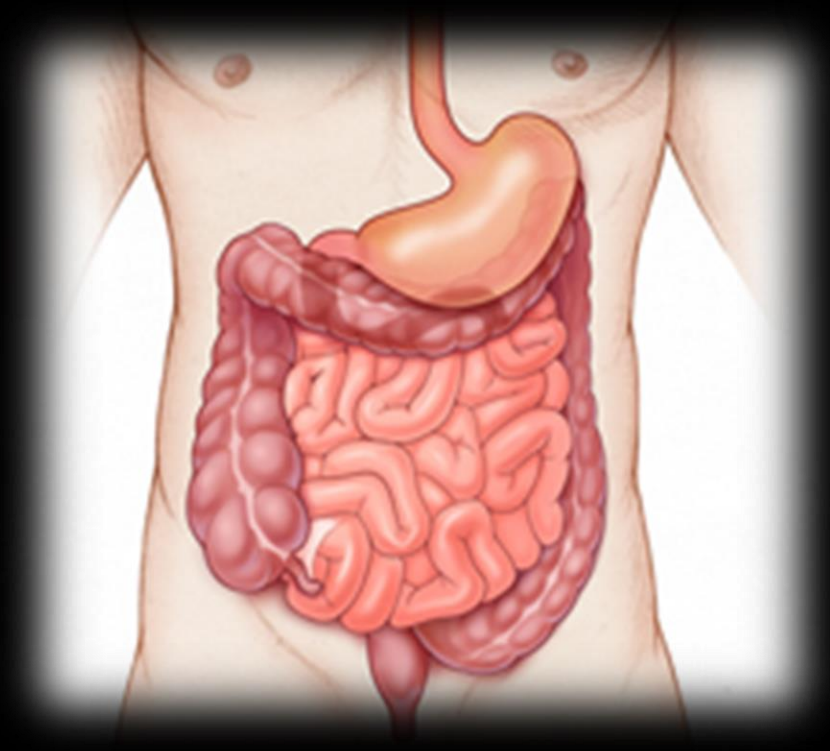
- As *V. Cholerae* enters and colonizes the stomach, it becomes sensitive to the stomach's acidic environment (pH = 2)

Mucosal secretions

- Mucus in our gut is a good source of immune cells including neutrophils, eosinophils, TNF-α, IL-1b, mast cells, lactoferrin, myeloperoxidase, and defensins, all of which are able to fight and destroy the pathogen
- More recently, invariant T cells have also been discovered in the mucosa that have potential of class switching antibody responses

Intestinal motility

- The gut's propulsive movement is another deterrent for *V. cholerae*, causing difficulty for the pathogen to adhere and colonize the epithelial walls



ADAPTIVE IMMUNE RESPONSE

Humoural Response
Predominant adaptive response

- B cell activated via exposure to *V. cholerae* antigen
- Antibody-producing plasma cells become activated
- Antigen presenting cells (APCs) – dendritic cells, macrophages, B cells – digest and present the pathogenic antigens
- Lymphocytes recognize the antigens presented on the APCs, activating the cellular mediated response
- Other key players involved:
  - IgA and IgG → protects the host against recurring cholera infections
  - Memory B cells → critical for long-term immunity as they circulate in the blood stream on the lookout for *V. cholerae*

Cell Mediated Response

- Initiation occurs via bacterial antigen recognition by T cells in the gastrointestinal mucosa, resulting in the production of plasma cells
- Antigen presenting cells (APCs), for instance dendritic cells and macrophages, present parts of the *V. cholerae* or its toxin to T lymphocytes, causing the production of cytotoxic T cells and natural killer (NK) cells
  - This cascade of events destroys the foreign pathogens
- Memory B cells, involved in long-term immunity against V. cholerae, are also differentiated from the B cell population

Question (ii)

Host damage: what damage ensues to the host from the immune response?

As our bodies are fighting against the *V. cholerae*, the resulting inflammatory response can cause severe damage to the host

Reactive species
- Reactive nitrogen or oxygen species are non-specific products of the inflammatory response. They have the ability to not only lyse the *V. cholerae*, but also cause **damage to the cells** of the host

Cytolysin secretion
- Cytolysin is secreted by the *V. cholerae*, and it increases epithelial cell permeability, resulting in **cell damage** and **lesions in the gut**

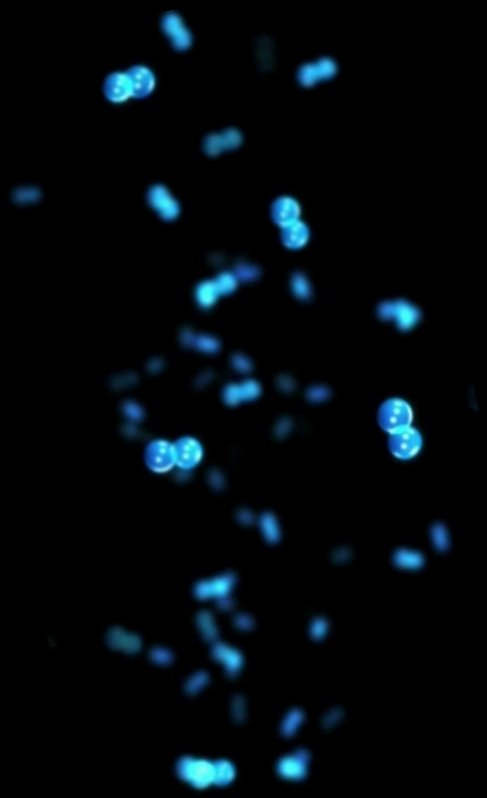
Septic shock
- This **fatal event** can occur in the case of several cholera infection. It is mediated by TNF-alpha and IL-1 when PAMPs are recognized by host PRRs

Cholera Toxin
- Disrupts adenylate cyclase pathway, causing efflux of water and ions (HCO3-, Na+, Cl-, K+) into small intestinal lumen, resulting in **diarrhea** and **severe dehydration**

Nephropathy
- Caused by accumulation of IgA in the renal glomerular mesangium, resulting in **kidney failure**

Question (iii)

Bacterial evasion: how does the bacteria attempt to evade these host response elements?

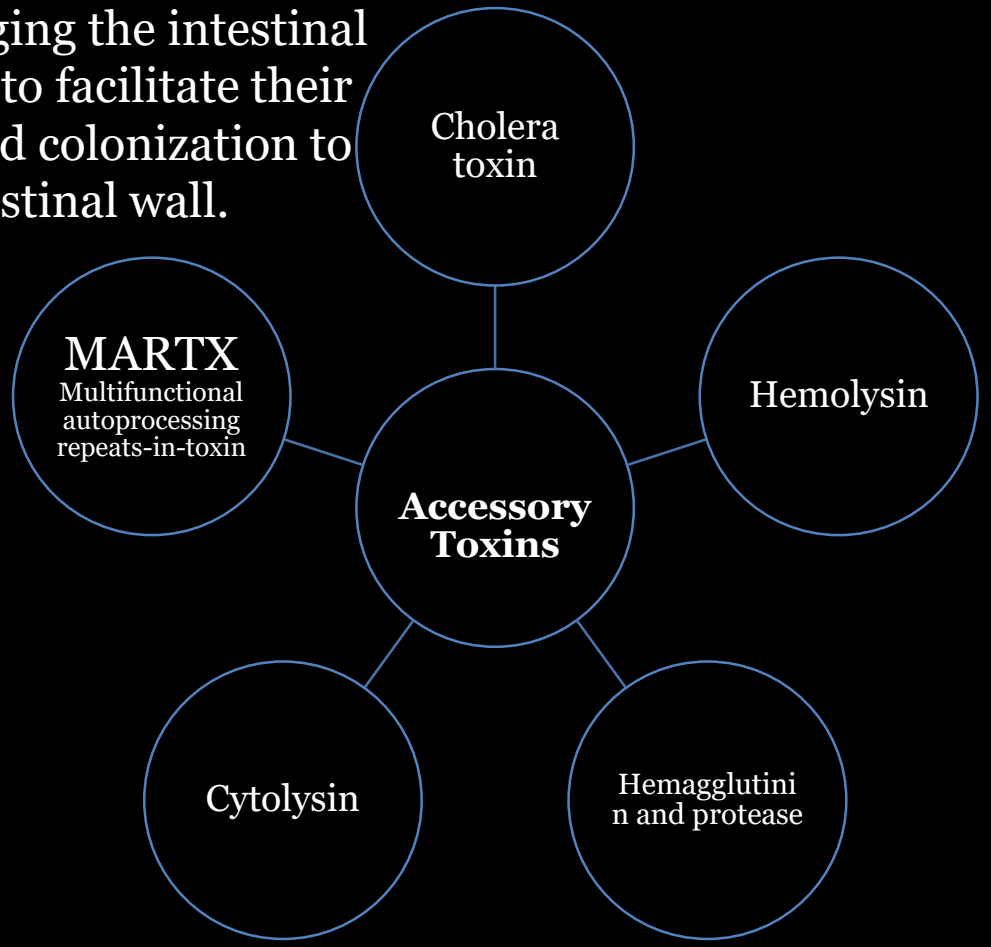


1. Accessory toxins
2. Secondary enterotoxins
3. Lipopolysaccharide
4. Extracellular matrix production
5. Quorum sensing and film production
6. Mannose Sensitive Hemagglutinin (MHSA)
7. Nuclease
8. Protein products
9. Adhering epithelial brush borders

Question (iii)

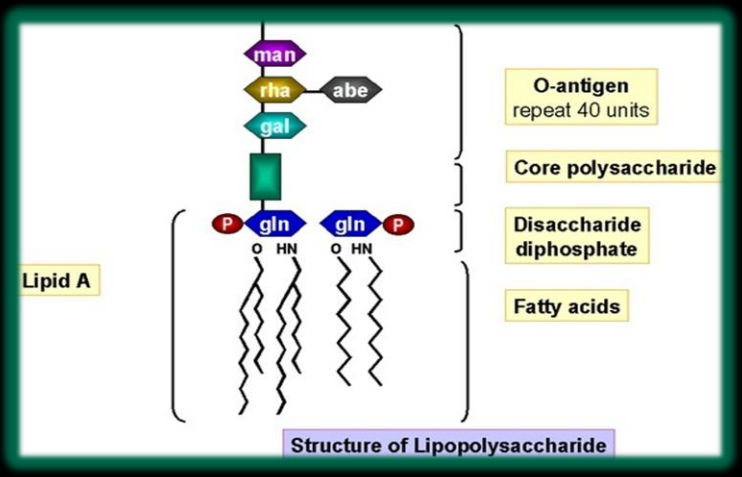
Bacterial evasion: how does the bacteria attempt to evade these host response elements?

1. **Accessory toxins** are secreted by the *V. cholerae*, and aid with changing the intestinal environment to facilitate their adherence and colonization to the intestinal wall.



2. The **secondary enterotoxin**, zona occludens toxin (ZOT), destroys the tight junctions of the epithelial cells within the small intestine, causing increased permeability, ultimately resulting in water and salt loss, as well as diarrhea.

3. **Lipopolysaccharide**, found on the outer membrane of and gram-negative bacteria, enables the pathogen to avoid phagocytosis via macrophages.



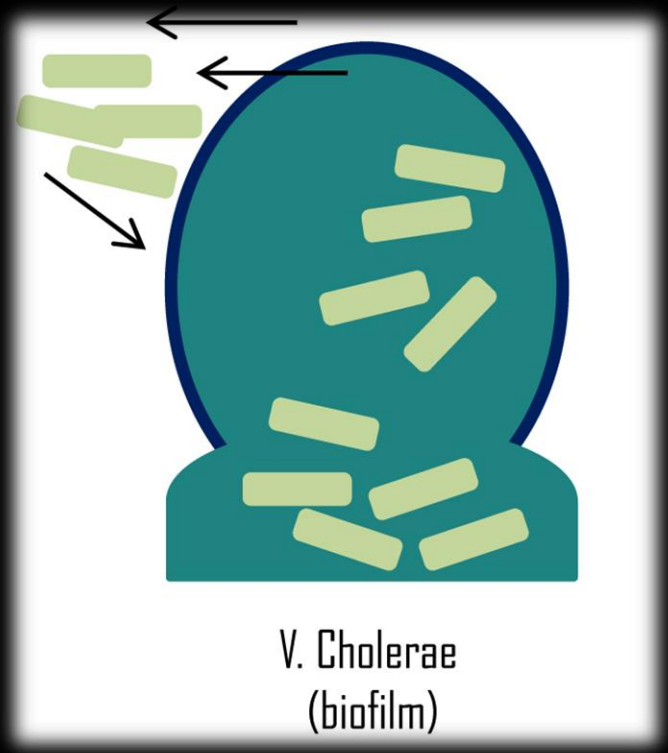
Question (iii)

Bacterial evasion: how does the bacteria attempt to evade these host response elements?

4. **Extracellular matrix**, consisting primarily of O-specific polysaccharide (OSP), acts as a barrier against complement-mediated attack for the *V. cholerae*. This ECM development occurs as a response to the anti-LPS antibodies present in the small intestine.

5. **Quorum sensing** is a method of communication for many bacteria, as it regulates a population's virulence gene expression and total cell density. As a result, quorum sensing regulators, LuxO and HapR, induce the formation of an extracellular polymeric matrix, **biofilm**.

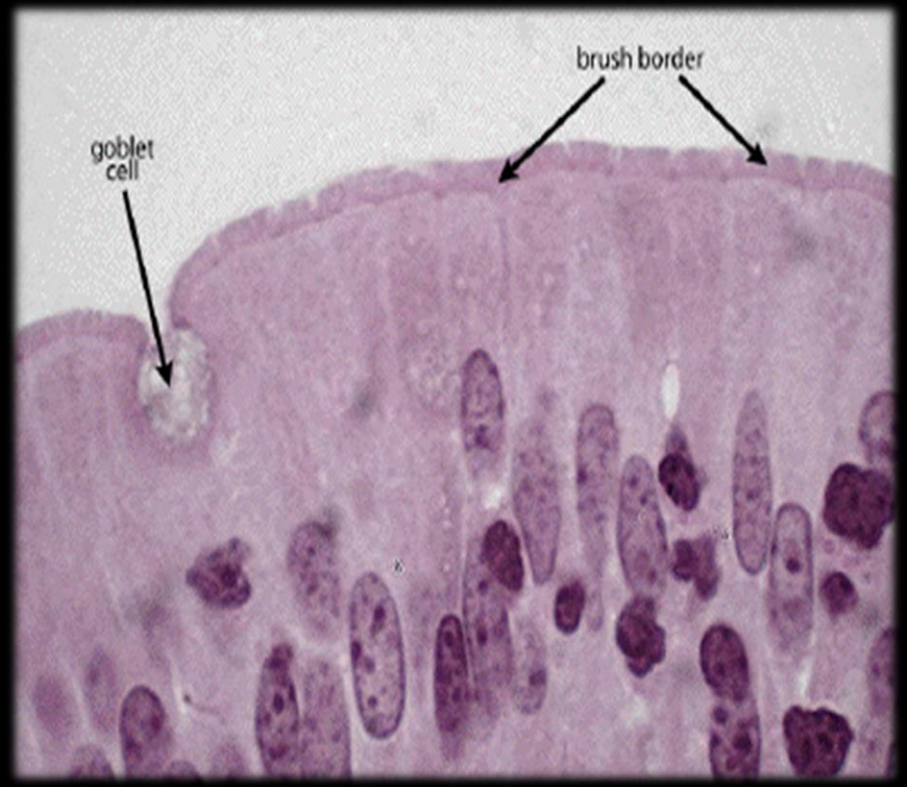
6. **Mannose sensitive hemagglutinin type IV pilus** downregulation occurs, permitting the *V. cholerae* to escape the recognition and binding from IgA of the adaptive immune response.



Biofilm acts as a protective barrier for the bacteria, preventing it from external host immune cells.

Question (iii)

Bacterial evasion: how does the bacteria attempt to evade these host response elements?



7. **Nucleases** Dns and Xds, secreted by the *V. cholerae*, allows it to evade the neutrophil extracellular traps (NETs) of the host innate response. These nucleases destroy the DNA of the NETs.

8. **Protein products**, such as hemagglutinin, are virulence factors of the *V. cholerae* that allow it to successfully colonize the small intestine of the host via facilitating adherence and degradation of host defense proteins.

9. V. cholerae's **adherence to brush border epithelial cells** allows the pathogen to survive the gastric motility and constant flow of fluids in the host.

Question (iv)

Is the bacteria completely removed, does the patient recover fully, and is there immunity to future infections from this particular bacteria ?

Treatments available for *V. cholerae* infected individuals

Rehydration therapy

To restore fluid balance

Zinc supplementation

Often used with rehydration therapy to reduce diarrhea

Antibiotics

(e.g. doxycycline, ciprofloxacin, azithromycin)

To kill residual bacteria

These treatments are often effective and successfully allow the patient to have a full recovery.

Question (iv)

Is the bacteria completely removed, does the patient recover fully, and is there immunity to future infections from this particular bacteria ?

- Though the treatments are effective, there is no guarantee that the *V. cholerae* has been completely expelled from the gut
  - At low concentrations, the presence of bacteria is often asymptomatic in the host
- Subsequent infections can occur, but this time the host can activate the immune response quicker, as the body already has the memory B cells to recognize the bacteria and its toxins → one would experience very little symptoms if any

- While there are several serotypes of *V. cholerae*, specific antibodies can only detect one serotype and not others due to slightly different antigens
  - If a patient is infected the second time by a different cholera serotype, no immunity is passed on from the first infection
- Studies have shown that circulating antibodies can provide immunity for up to **3 years**, but life-long immunity can not be developed