

LOG BOOK.

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THE ARK.

In this odyssey, we follow *Salmonella* Typhi re-imagined as a fleet of submarines, swimming through the vast waters of Dublin Bay. They are searching for a human host, or 'ark'. *Salmonella* Typhi are tiny (3-5 um long) capsule-shaped bacteria that can swim using long, rotating tails called flagella. For them to find a suitable mouth or nose to enter the body is like looking for a needle in a haystack, if you were the size of a grain of sand. And finding a host is just the first challenge they face. Let the journey begin...

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CAVERN

Once ingested, the Typhi fleet must survive being swallowed and exposure to stomach acid and digestive enzymes, before getting into the real interior of the human body, through the gut. The gut is a thronging thoroughfare where the outside meets the inside. Inside these long tunnels live all sorts of microbes, protecting their host from pathogens by competing for space and nutrients. In return for a place to live, they also provide us with specific nutrients and help us absorb our food. We have re-imagined this microbial metropolis as a busy port city, like Dublin, but made from the very ships that founded it. Can you spot the Customs House, and the Poolbeg towers in there?

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FOREST

The microbes in our guts don't live directly on the gut walls, but on a layer of thick mucus or 'sludge' lining the walls. They are tethered to the mucus (re-imagined as anchors) in groups. Breaking through the thick mucus layer is near impossible for many bacteria, but not for *Salmonella* Typhi. Beneath the thick mucus, there is a second thinner layer of mucus that coats a single layer of gut cells with 'long limbless trees' called microvilli, which increase gut nutrient absorption.

In this forest of limbless trees are areas, called Peyer's patches, where microvilli are much shorter. These 'meadowlike clearings' are the real gateway to the internal human body or 'undercity'. *Salmonella* Typhi can attach to these surfaces, detach their flagella and then inject proteins into the gut cells (front right). These proteins re-model the gut cell shape to allow *Salmonella* Typhi to pass through them (pictured at the centre back).

These sites are also used by our immune system to sample what is going on in the gut – host immune cells poke through the gut cell layer like a hand, to grab and taste whatever is on the other side. Pictured on the left at the back, being grabbed by an immune cell is another way for *Salmonella* Typhi to get our body's undercity.

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UNDERCITY.

The 'undercity' is the area underneath the gut lining. Known as the sub-mucosa, this area is packed with immune cells, or 'ark patrol vessels', on the lookout for invading pathogens. While some of these cells reach through the gut walls to sample what is on the other side, the rest of the immune cells are first responders, there to act quickly if they see any invaders or if the alarm is raised. *Salmonella* Typhi evades detection by coating itself in a capsule, re-imagined here as dazzle camouflage, to hide from the immune cells. They also produce typhoid toxin, which dulls the immune cells – they become slow to notice and respond. Capsule and toxin production is key to protect *Salmonella* Typhi for long enough to multiply here and spread.

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HIJACK.

Despite the protection of camouflage and toxins, *Salmonella* Typhi are not safe for long in the undercity; it is a vipers' nest of immune activity. *Salmonella* Typhi have another weapon in their arsenal – they can inject immune cells called macrophages – large eaters – with proteins to re-program them. The risks are considerable. *Salmonella* Typhi have to shed their camouflage to force their own uptake by the ark's macrophage 'defensive cruisers'. If the macrophage re-programming doesn't work before the Typhi bacteria are spotted, they will be digested into tiny pieces and the macrophage will enter battle mode. All immune cells will start eating everything and call for reinforcements. However, if *Salmonella* Typhi get it right, they can produce even more toxin and safely travel through the body.

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PASSAGEWAYS

From the undercity, *Salmonella* Typhi can enter the immune superhighway, the lymphatics, which leads to every part of the body. To travel safely through the lymphatic passageways, *Salmonella* Typhi has to either be camouflaged in its capsule, or hitching a ride inside a macrophage immune cell. We have re-imagined the lymphatics as signposted tunnels, from the point of view of a *Salmonella* Typhi submarine bridge. In reality, there are no signposts, only the power of numbers. Once *Salmonella* Typhi have found a new base, (in the liver, spleen, or bone marrow), they start reproducing in large numbers and can be found in the bloodstream. This is when human hosts notice something is wrong: immune defences go into full battle mode, causing a high fever, while new generations of Typhi bacteria spread and wreak more havoc. In their attempt to break back into the gut, large numbers of *Salmonella* Typhi damage the gut walls around the Peyer's patches and – in the worst case – allow other gut bacteria to enter the bloodstream. Feverish patients experience stomach pains, intestinal bleeding, and are at risk of sepsis. If untreated, around one in five patients die.

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PLANETOIDS.

While some *Salmonella* Typhi are fighting immune cells and causing chaos to return to the gut, others may stumble upon a more favourable place to hide. Welcome to the gallbladder, complete with gallstone 'planetoids'. The sticky surfaces of these planetoids offer an ideal home where *Salmonella* Typhi can live and multiply indefinitely, without the body's immune system noticing. Thriving in the digestive bile that is stored in the gallbladder, *Salmonella* Typhi can grow densely on the gallstones, forming biofilm cities. There is also an exit route to find new bases without harming the host - gallstone biofilms shed *Salmonella* Typhi at low levels, allowing them to return to the gut along the bile duct with the digestive juices that are released to digest each meal. Around five percent of acute infections can result in long-term Typhi colonisation, with human carriers shedding *Salmonella* Typhi while seeming completely healthy.

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RETURN.

Salmonella Typhi's journey is endless. To continue to survive as a species, descendants of our fleet must re-emerge from the passageways and hidden spaces of the human body into the open. This involves travelling to the end of the gut and being pushed out into the bright world outside, via the anus (top left). Once outside, finding a new ark is essential. In this particular odyssey, *Salmonella* Typhi gets flushed out with the rest of the faeces (top right) and so on into the Liffey (bottom left). In Edwardian times, high levels of faecal contamination and inadequate water infrastructure meant that bacteria such as Typhi could make their way into drinking water or water used for food preparation. A perfect cycle of infection (bottom right).