L08

Recap

Microbes-Humans interactions:

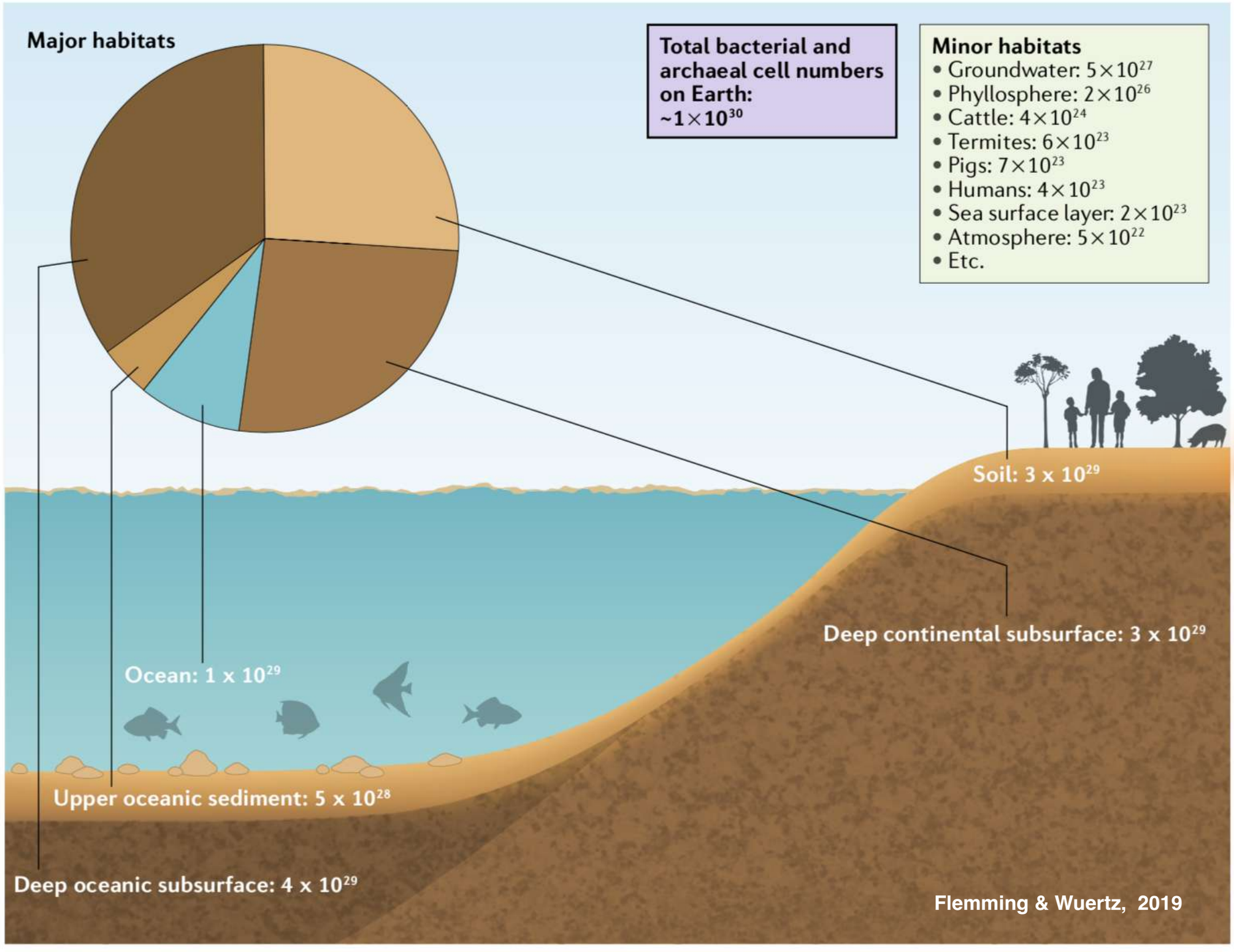
Infections, pathogenicity & OneHealth

Infections & pathogenicity

Bacterial pathogenesis is the process by which bacteria infect and cause disease in a host

Not all bacteria are pathogens and have the ability for pathogenesis (also known as virulence)

Earth is inhabited by 10^{11}–10^{12} microbial species (Locey & Lennon, 2016)



~1,400 known species of human pathogens

Microbial infection and disease

- Only a small percentage of the world's bacteria cause infection and disease
- Bacterial infections have a **large impact** on public health
- In total, there are ~1,400 known species of human pathogens (including viruses, bacteria, fungi, protozoa and helminths)
- Human pathogens account for much **less than 1%** of the total number of microbial species on the planet

Key points, I

- A **pathogen** is a micro-organism that has the potential to cause disease

- An **infection is the invasion and multiplication** of pathogenic microbes in an individual or population

- **Disease** is when the infection causes **damage** to the individual's vital functions or systems

- *An infection does not always result in disease!*

- To cause an **infection, microbes must enter human bodies**

- The site at which they enter is known as the **portal of entry**

Definitions, I

- **Infection** is host invasion by microorganisms, which then multiply in close association with host's tissues

- Infection is distinguished from **disease**, a morbid process that does not necessarily involve infection

- **The capacity of a bacterium to cause disease reflects its relative pathogenicity**

- **Pathogenicity is a measure of the potential for an infectious organism to cause disease**

- **Pathogenesis** refers both to the mechanism of infection and to the mechanism by which disease develops

- **Virulence** describes the organism's propensity to cause disease, through properties such as invasiveness and toxin production

Key points, II

- Microbes can **enter** the human/animal body through the four sites listed below:

A. **Respiratory** tract (mouth and nose) e.g. influenza virus which causes the flu

B. **Gastrointestinal** tract (mouth oral cavity) e.g. *Vibrio cholerae* which causes cholera

C. **Urogenital** tract e.g. *Escherichia coli* which causes cystitis

D. **Breaks in the skin surface** e.g. *Clostridium tetani* which causes tetanus

Portal of entry

Bacteria: Human Microbiome, Infection & Spread – Microbiology | Lecturio

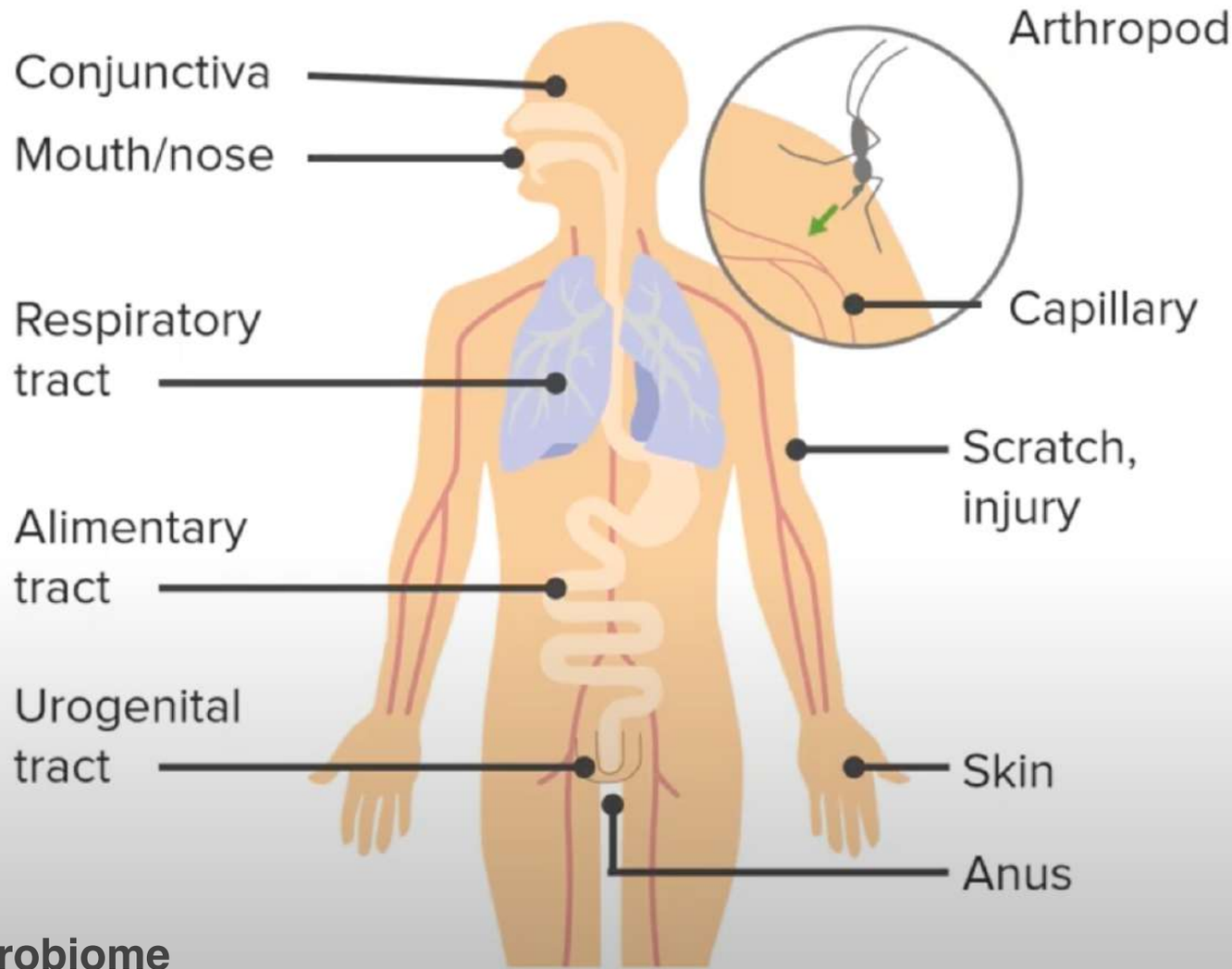
Gaining Entry

Mucous membranes

- Breathing, eating, sex
- Cholera, whooping cough, gonorrhea

Penetration

- Invasion into cells, tissues
- Insect bites
- Scratch, injury



Prof. Dr. Vincent Racaniello; http://lectur.io/microbiome

Gastrointestinal tract

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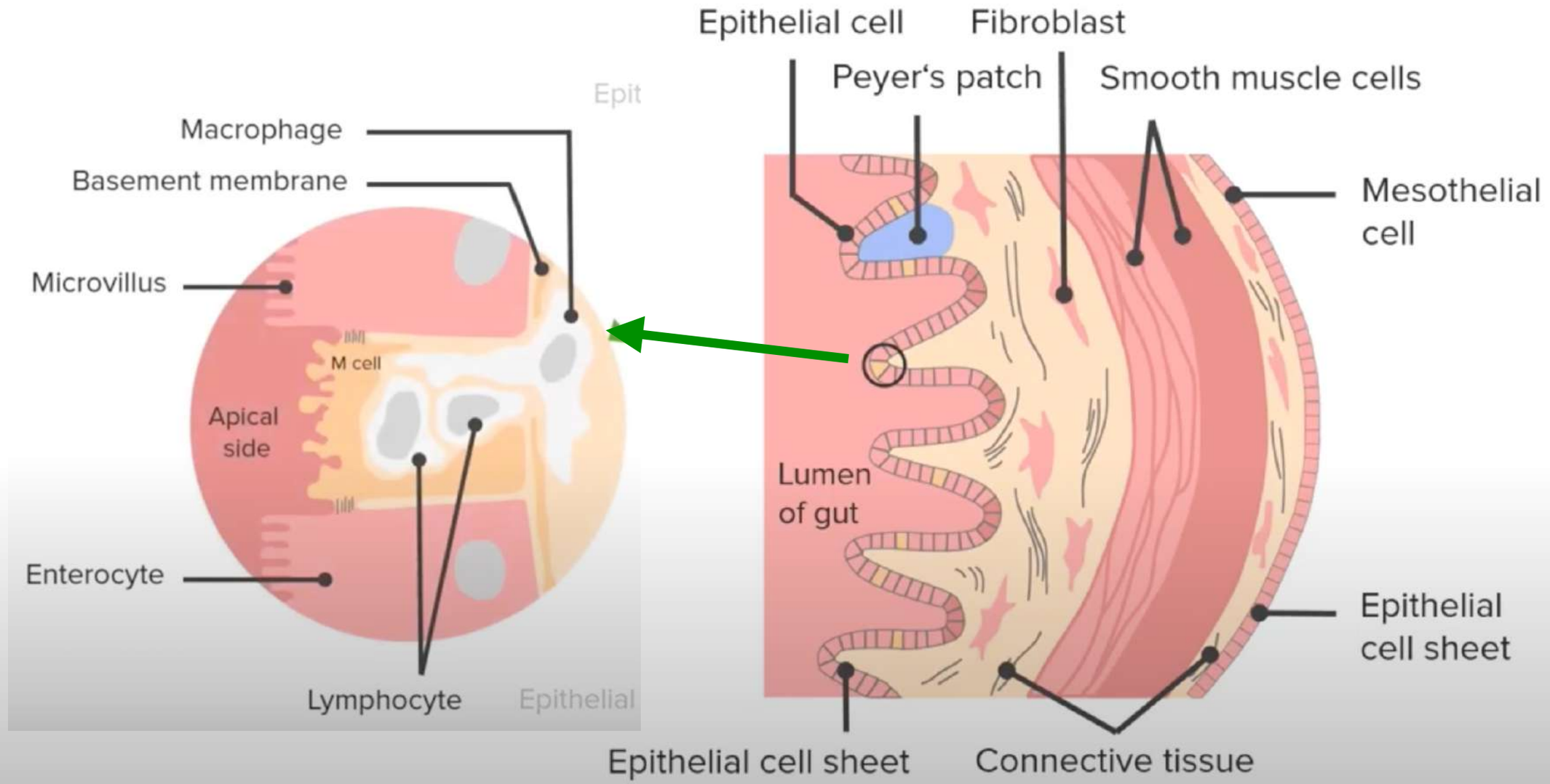
Spread



Prof. Dr. Vincent Racaniello; http://lectur.io/microbiome

Key points, III

To make HUMANS, ANIMAL, PLANTS ill/sick microbes have to:

A. Reach their **target** site in the body

B. **Attach** to the target site they are trying to infect so that they are not dislodged

C. Multiply rapidly

D. **Obtain** their **nutrients** from the host

E. Avoid and survive attack by the host's immune system

ROUTES OF TRANSMISSION

- The **spreading** of microbes is called **transmission**

Transmission involves the following stages:

A. Escape from the host or reservoir of infection (where the infectious agent normally lives and multiplies)

B. Transport to the new host

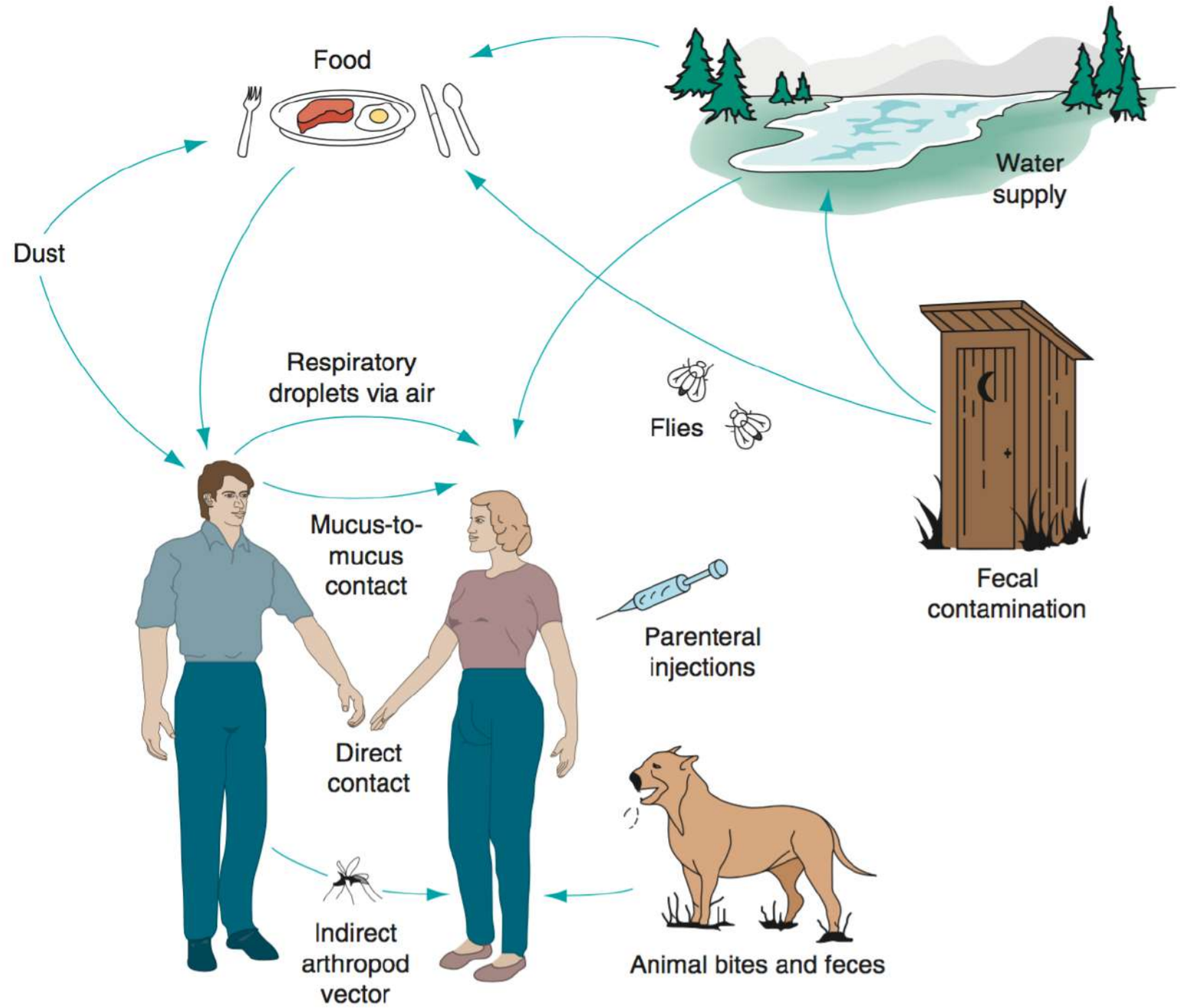
C. Entry to the new host

D. Escape from the new host

E. Different pathogens have different modes of transmission —> For example respiratory pathogens are usually airborne and intestinal pathogens are usually spread by water or food

Mode of disease transmission

Understanding mechanisms of transmission is important not only because it helps control those diseases that emerge but also because it provides opportunities to control multiple diseases transmitted by the same mechanisms



Doreen & Gorbach, 2008

Figure 5 Modes of disease transmission. Reproduced with permission from Engelkirk PG and Burton GR (eds.) (2006) Epidemiology and public health. In: *Burton's Microbiology for the Health Sciences*, 8th edn., ch. 11. Baltimore: Lippincott Williams and Wilkins.

Source of water contamination

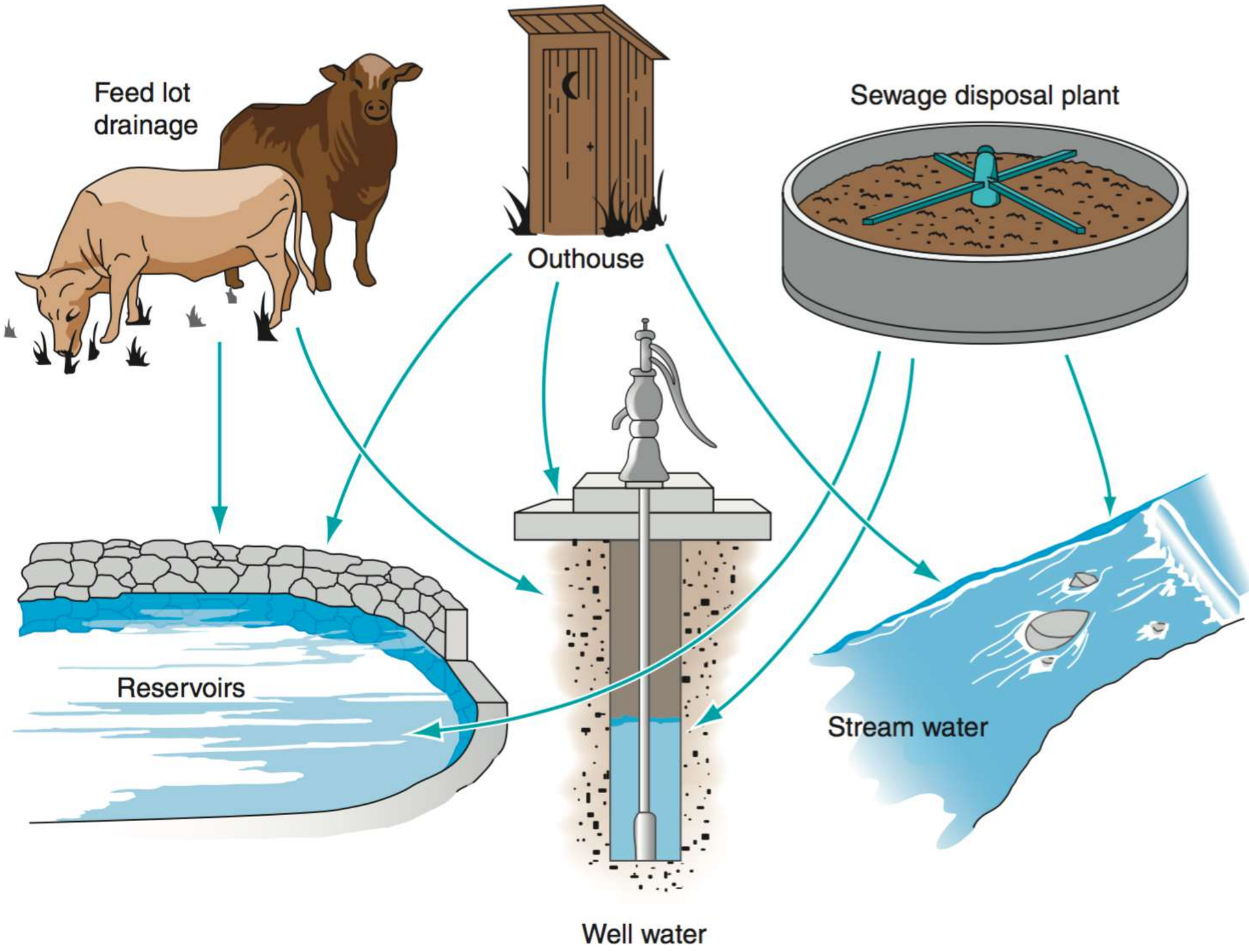


Figure 4 Sources of water contamination. Reproduced with permission from Engelkirk PG and Burton GR (eds.) (2006) Epidemiology and public health. In: *Burton's Microbiology for the Health Sciences*, 8th edn., ch. 11. Baltimore: Lippincott Williams and Wilkins.

Table 1 Reservoirs for bacteria

Reservoirs	*Disease examples*
Human	Typhoid fever, syphilis
Animal	Anthrax (cows), *Salmonella* (turtles), tularemia (rabbits), Lyme disease (white-footed mice)
Arthropods	Rocky Mountain spotted fever (ticks), endemic typhus (fleas), scrub typhus (mites)
Air	Tuberculosis
Soil	Tetanus, botulism, gas gangrene
Food	Vibrio, *E. coli* 0157:H7
Water	Shigella, Legionella

Doreen & Gorbach, 2008

Table 2 Modes of transmission of bacterial infections

Mode of transmission	*Disease examples*
Contact	Streptococcal impetigo (skin-to-skin), gonorrhea (mucus membrane-to-mucus membrane), *Salmonella* (fecal–oral), syphilis (transfusion)
Airborne	Tuberculosis, Q fever, legionella
Droplet	Pertussis, meningococcus, *Haemophilus influenzae*
Vectors	Lyme disease (tick), Shigella (fly) epidemic typhus (lice), bubonic plague (fleas)
Vehicular	*Campylobacter* (food), trachoma (fomites)

Doreen & Gorbach, 2008

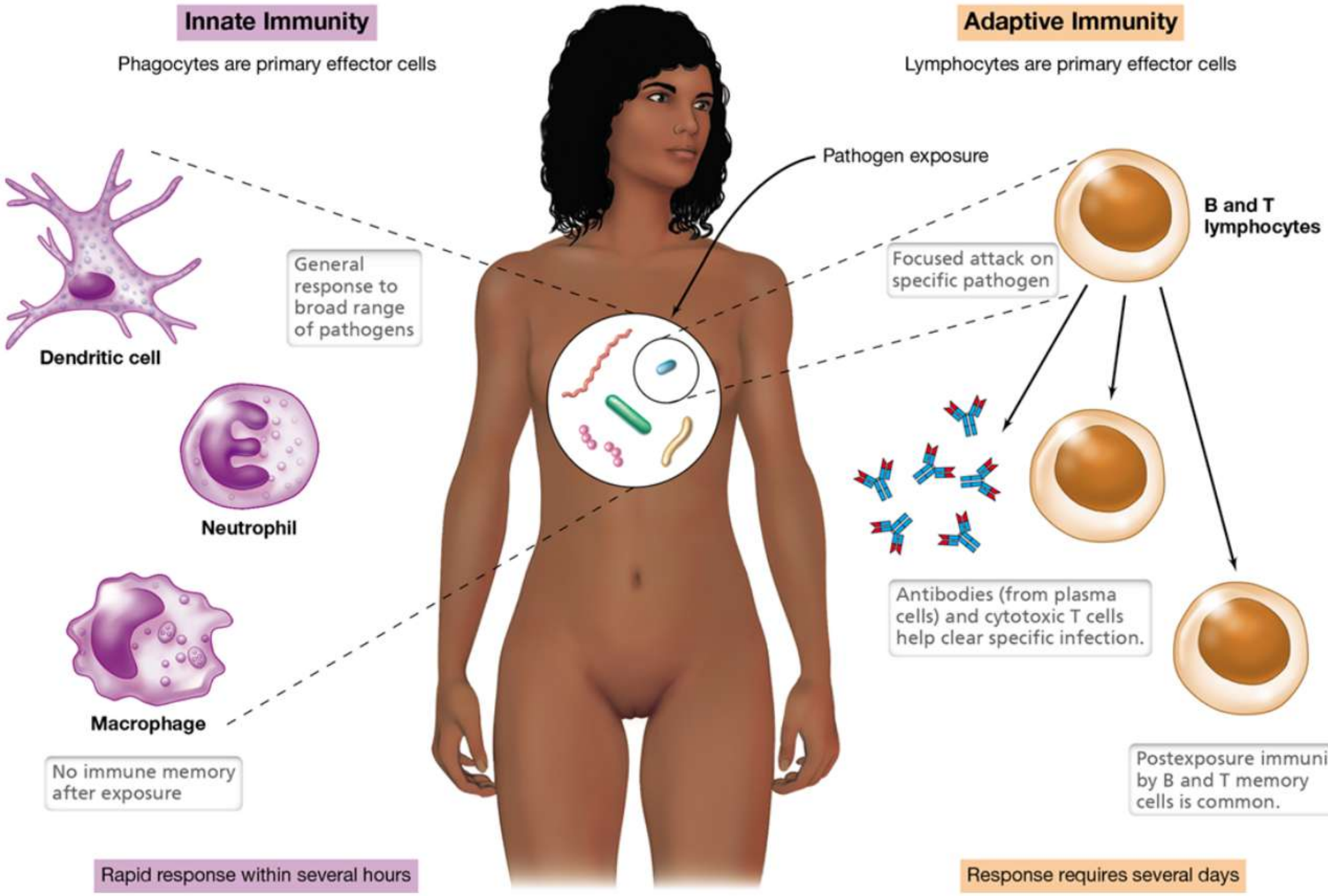
MICROBIAL BATTLEFIELD

IMMUNE SYSTEM

- An infection can be seen as a battle between the invading pathogens and the host
- Our bodies are equipped to fight off invading microbes that may cause disease
- The immune response has to be tightly controlled to ensure a clearance of the bacteria but also to prevent tissue damage and necrosis as result of sepsis
- These are called our natural defences

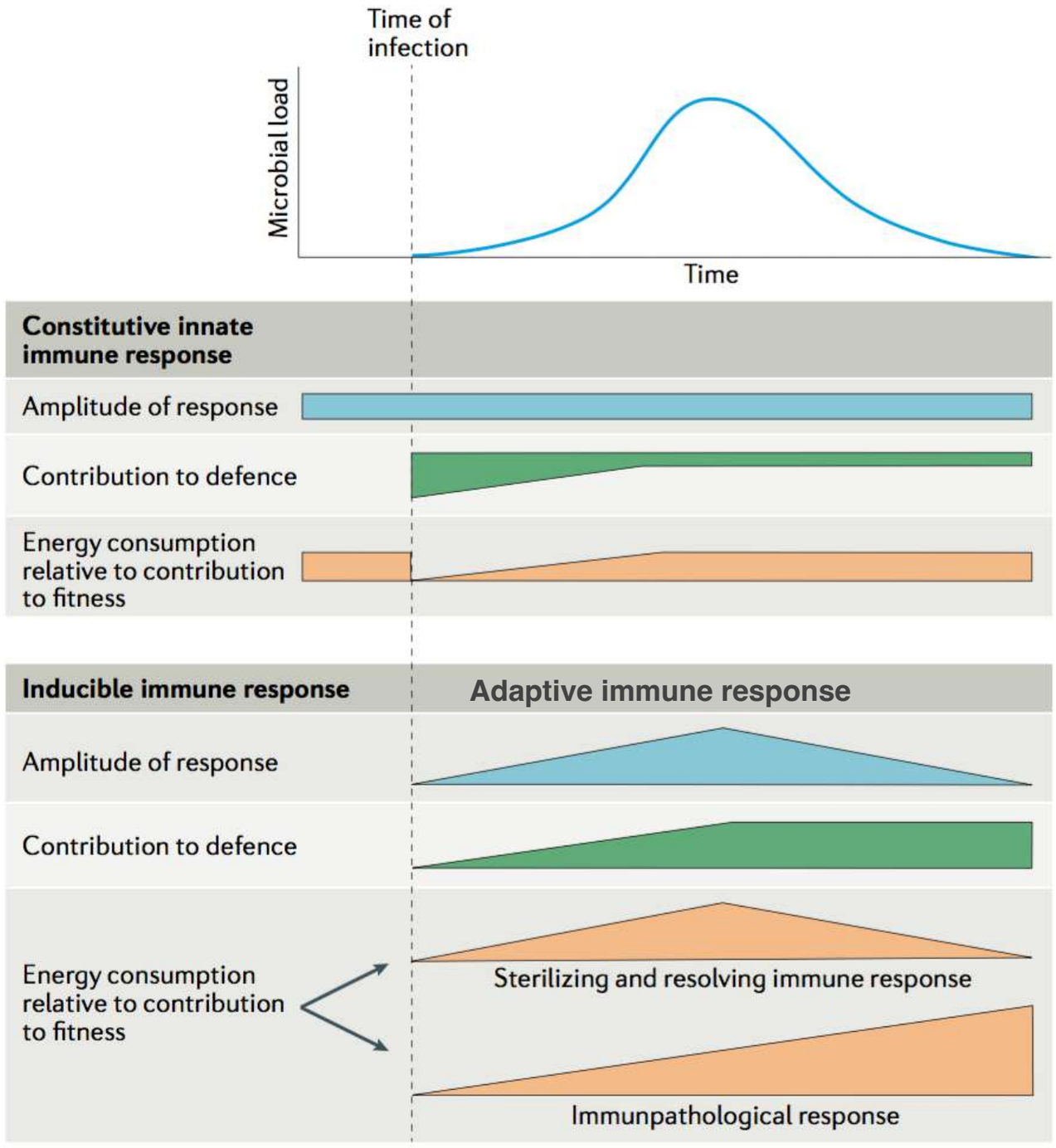
1. Aspecific defense: chemical and physical barriers
2. Costitutive / innate
3. Adaptive / inducible

Innate/Constitutive *vs* Adaptive/Inducible immunity



Madigan, 2020

Innate/Constitutive immune responses versus inducible/adaptive immune responses



- **Amplitude of response**
- **Contribution to defense**
- **Energy consumption**

a. Sterilizing and resolving immune response, the additional energy consumption required by the inducible immune response is balanced by the re-establishment of homeostasis

b. Immunopathological response, the energy that is consumed to mount an inducible response does not benefit the host and instead leads to tissue damage and disruption of homeostasis

Paludan et al., 2021

Virulence and microbial structures

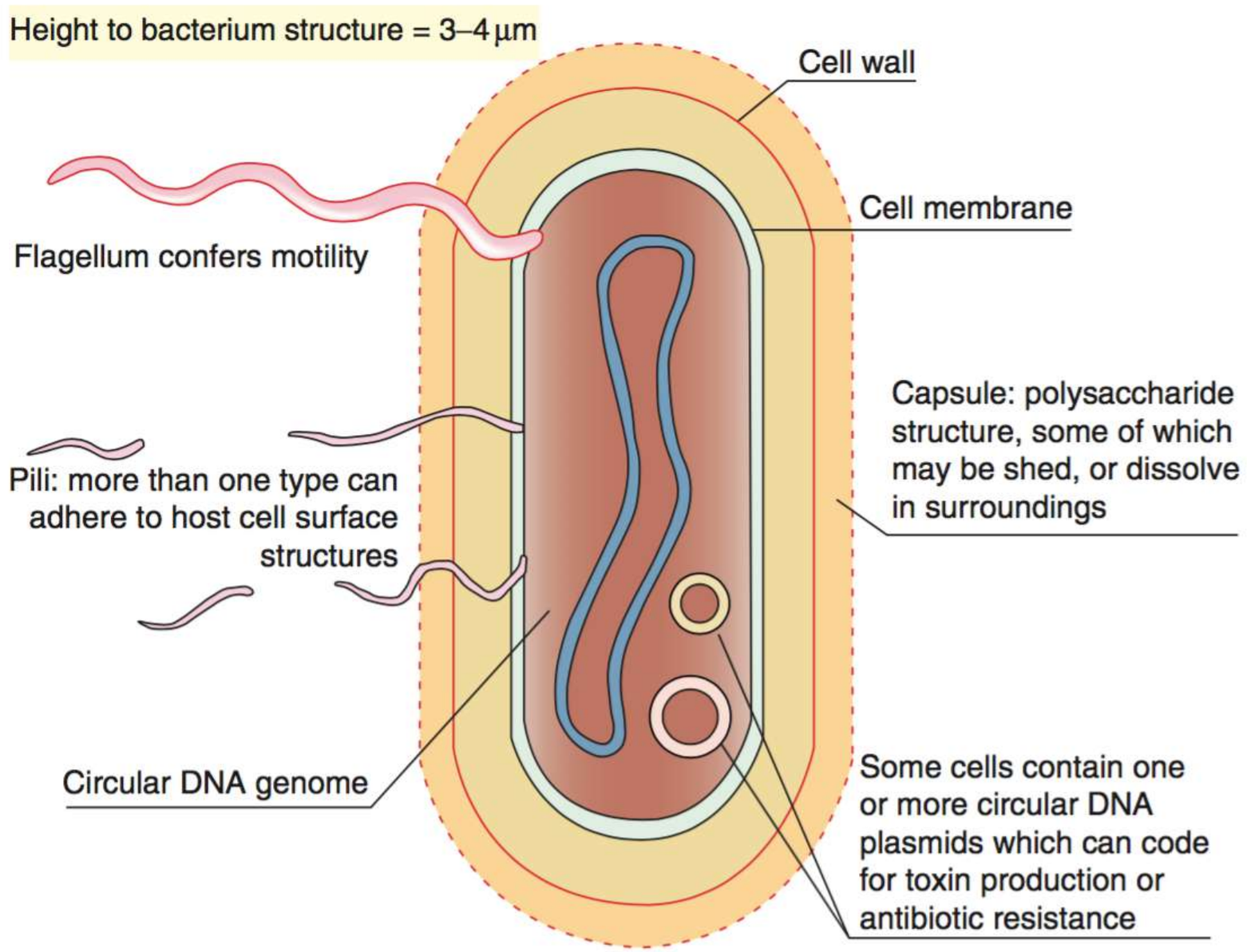


Figure 1 Structure of a bacterium. Reproduced from Bannister BA, Begg NT, and Gillespie SH (eds.) (1996) Structure and classification of pathogens. In: *Infectious Disease*, 2nd edn., ch. 2, pp. 23–34. Oxford, UK: Blackwell Science Ltd., with permission from Blackwell Publishing.

Virulence Factors

Adherence Factors: Many pathogenic bacteria colonize mucosal sites by using pili (fimbriae) to adhere to cells.

Invasion Factors: Surface components that allow the bacterium to invade host cells can be encoded on plasmids, but more often are on the chromosome.

Capsules: Many bacteria are surrounded by capsules that protect them from opsonization and phagocytosis.

Endotoxins: The lipopolysaccharide endotoxins on Gram-negative bacteria cause fever, changes in blood pressure, inflammation, lethal shock, and many other toxic events.

Exotoxins: Exotoxins include several types of protein toxins and enzymes produced and/or secreted from pathogenic bacteria. Major categories include cytotoxins, neurotoxins, and enterotoxins.

Siderophores: Siderophores are iron-binding factors that allow some bacteria to compete with the host for iron, which is bound to hemoglobin, transferrin, and lactoferrin.

Virulence, I

- Bacterial **virulence**: the “relative capacity to **overcome available defenses**” (Sparling, 1983), or “the relative capacity of a microorganism **to cause damage in a host**” (Casadevall and Pirofski, 2003)

- This capability is mediated by **virulence genes/factors**, which have to fulfill three requirements:

(i) **active** in the **interaction** between pathogen and host

(ii) **direct determinants** of the pathogen damage

(iii) the **lack** of those virulence genes **in non-pathogenic strains** (Wassenaar and Gaastra, 2001)

Virulence, II

- Virulence as a concept is **intrinsically coupled to disease**
- **Degree of host injury** does **not** necessarily correlate with **evolutionary success** for a pathogenic microbe
- **Survival and multiplication** are clearly the **priorities** for the **microbe**
- **Disease is simply a manifestation** of the complex interactions required to accomplish these two goals within the milieu of host tissues
- Competition for the same resources: nutrients and energy
- Virulence determinants which includes all those **factors contributing to infection** and to **disease**, with the **exception of "housekeeping**" functions that are required for efficient multiplication on non living substrates
- The **virulence** of bacterial pathogens is a **complex, multifactorial process** requiring the **coordinated activity of many bacterial gene products**

Virulence, III

Why be virulent?

Hypothesis: virulence is an **unavoidable cost or side effect** of **growing within a host and transmitting to the next host**, and is maintained as the result of a ***trade-off between the costs of host pathology and the benefits of transmission to a new host***

Other hypotheses highlight the **importance of selection in non-disease settings**, where **alternative functions of virulence factors can coincidentally select for virulence factor-induced damage to human hosts**

Virulence factors are **molecular determinants** of virulence; they are pathogen components that are **non-essential to *in vitro* growth in rich media** but cause increased virulence during infection of a host

Virulence, IV

- **MGEs** are also responsible for the movement of antimicrobial-resistance determinants and virulence factors between microbes
- **Epigenetic regulation** of virulence factor via orphan methyltrasferase (Dam)
- **Quorum sensing** regulation of population level behavior (one cell does not harm—>coordinated behavior powerful weapon)
- **Two-component system** regulates virulence
- The **effects of virulence-factor expression on pathogen fitness** (net growth colony based) can be variable, particularly between sites of infection and commensal or environmental sites immediate
- **Private benefit to the (focal) bacterium** that expresses the trait (*e.g.* adhesins) and collectively beneficial virulence factors that confer a **benefit to a group or neighbourhood of bacteria** (*e.g.* secreted siderophores, enzymes and toxins)
- '**Cooperative' category**, which is characterized by the secretion of costly molecules that scavenge, digest or liberate resources that promote growth

SELF or NON-SELF

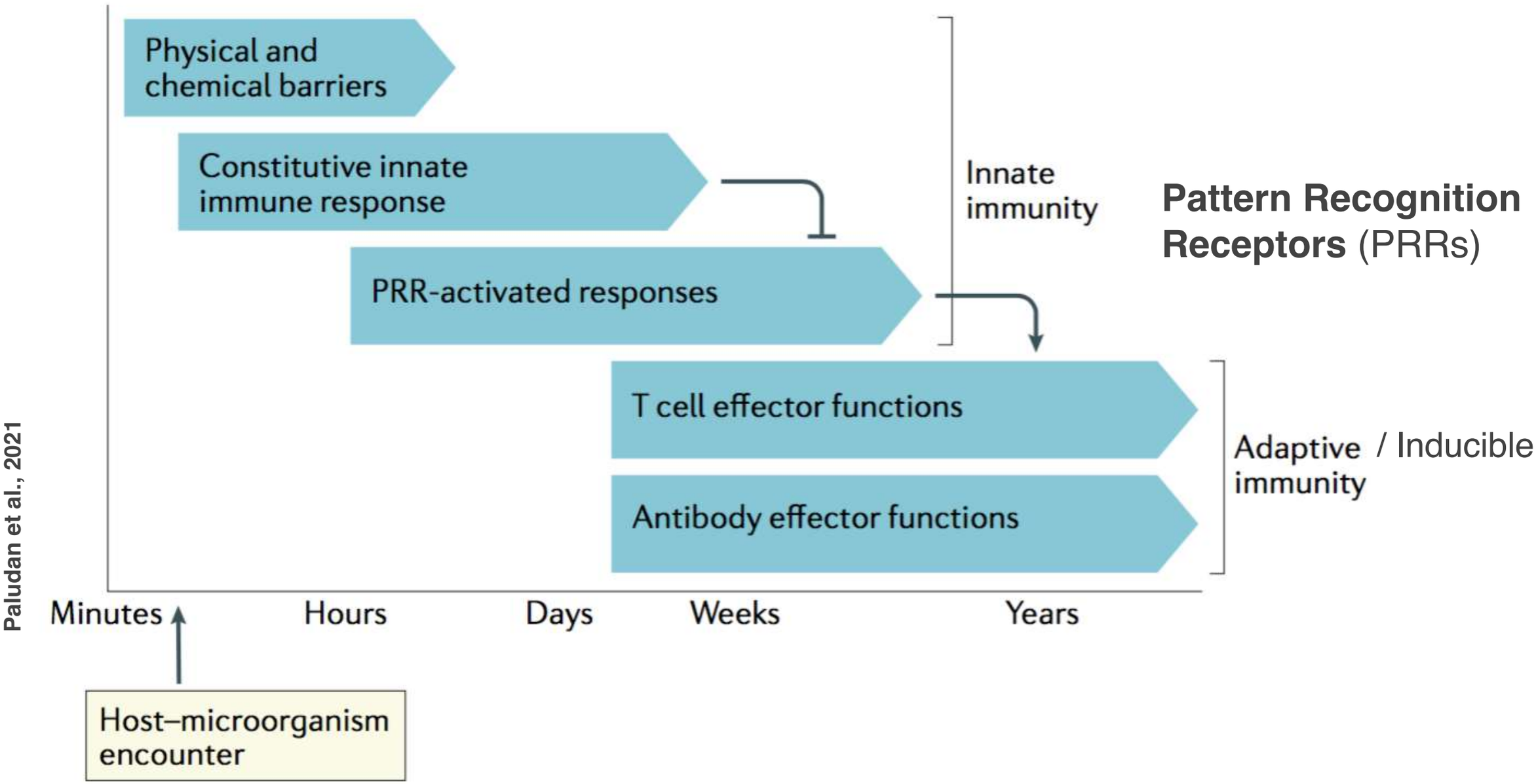
The innate immune system has the capacity to detect '**non-self**' molecules derived from pathogens, known as **pathogen-associated molecular patterns, via pattern recognition receptors**

The self–non-self theory was first formulated by Frank Macfarlane Burnet in **1959** and was refined in 1989, when Charles Janeway proposed the '**pattern recognition**' theory

It postulated that innate immune cells express distinct germ-line-encoded **pattern recognition receptors (PRRs) that recognize conserved pathogen-associated molecular patterns (PAMPs) unique to microbes**

The recognition of **DAMPs,** which are produced or released by **damaged and dying cells, promotes sterile inflammation**, which is important for **tissue repair and regeneration**, but can also lead to the development of numerous inflammatory diseases, such as metabolic disorders, neurodegenerative diseases, autoimmune diseases and cancer

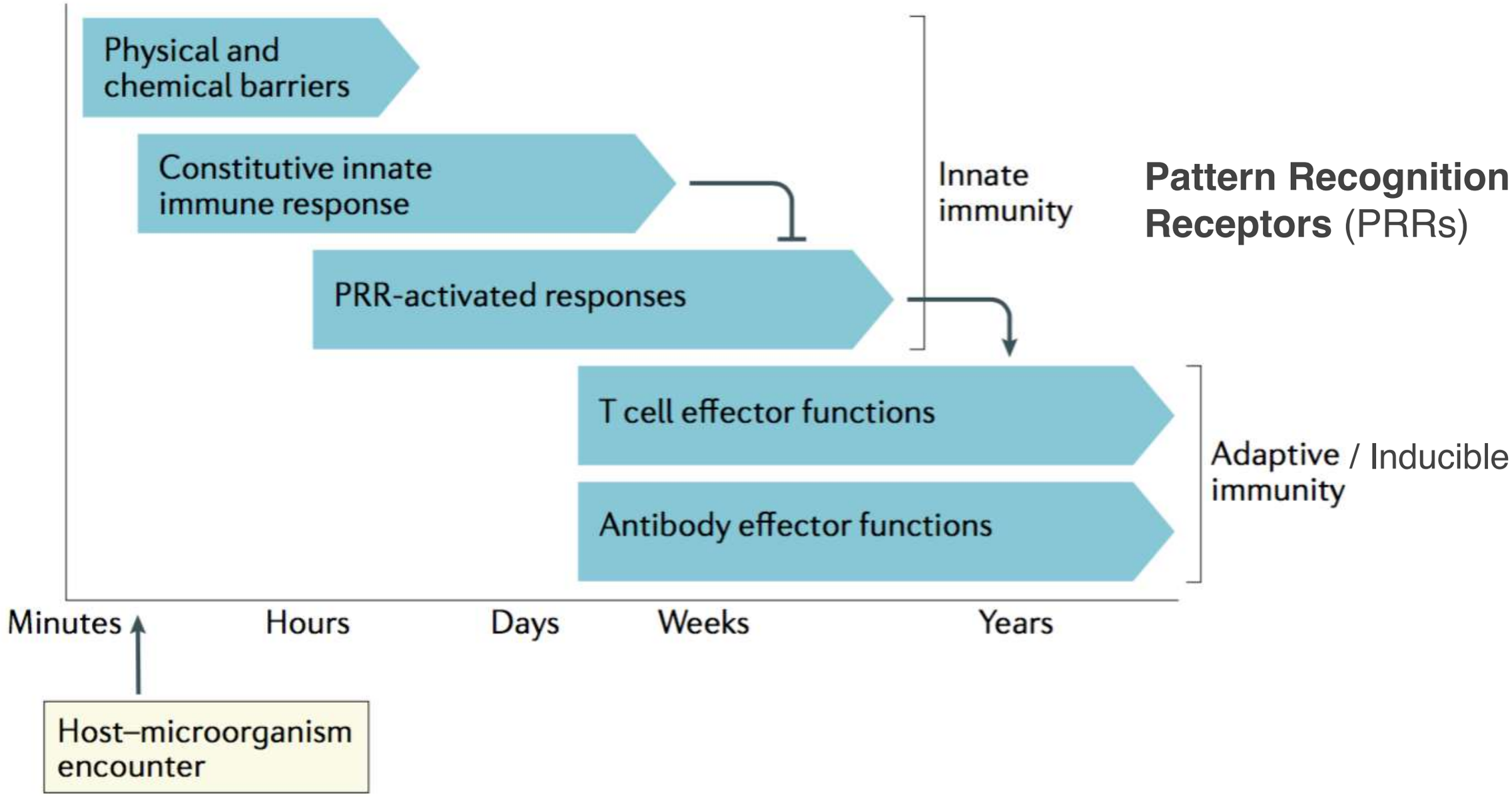
Time relationship between the different layers of the immune response



Paludan et al., 2021

- A first layer of defence is exerted by **physical and chemical barriers**
- Constitutive **innate immune mechanisms** function as soon as a danger **signal is detected** and eliminate harmful microorganisms and host molecules **by specific non-inflammatory mechanisms** that **operate independently of PRRs**

Time relationship between the different layers of the immune response



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Pattern Recognition Receptors (PRRs)

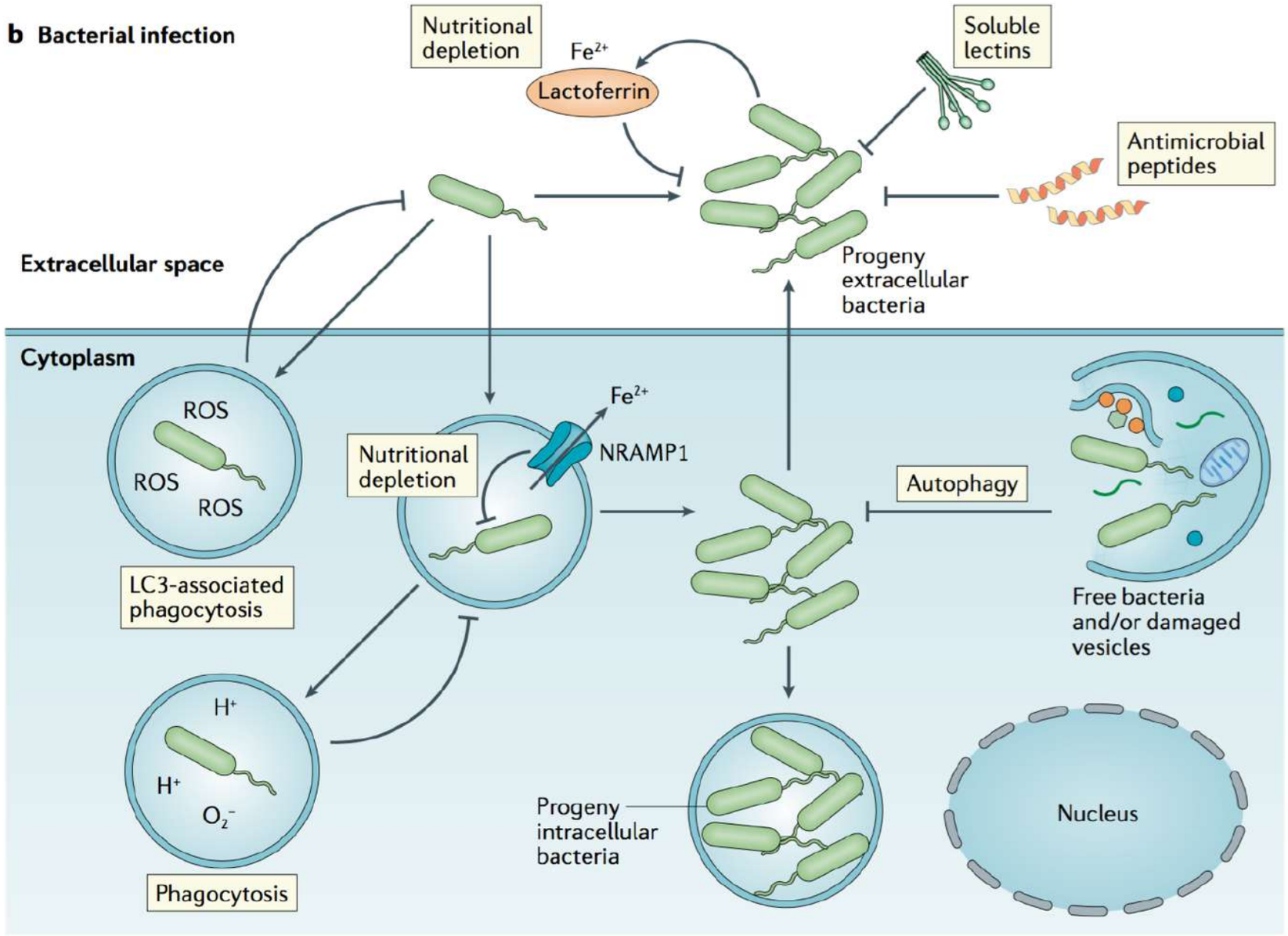
- **Constitutive innate immune** response inhibit establishment of the infection and accumulation of **PAMP**s (**Pathogen-Associated-Molecular Pattern**) and **DAMP**s (**Damage-Associated-Molecular Pattern**), thus **limiting the activation of PRR-based** inducible innate immune responses
- **If PRR-based immunity is activated**, owing to the level of PAMPs exceeding a certain threshold, this leads to inflammation and **promotes activation of the adaptive/inducible immune response** mediated by T cells and antibodies

First encounter

Pathogen recognition by extracellular or endosomal receptors

Constitutive innate immune response

- **Host cell uses bacterial compartmentalization, oxidative and nutrient stress, antimicrobial peptides**, lysosome-mediate degradation, autophagy, inflammasome activation and pyroptosis to kill the pathogens
- Some intracellular pathogens can control the signalling pathways activated by host receptors, **interact with endocytic pathway, escape** from the phagosome, **inhibit fusion with lysosomes, manipulate vesicular trafficking and avoid autophagosome degradation and inflammasome activation**



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Targeting microbial replication

Direct inhibition of microbial replication is executed by molecules that interfere with specific steps in the replication cycle of a given microorganism. There are at least six mechanisms of action in this category: restriction factors that directly block a **specific replication step**; **restriction factors that deplete molecules essential for replication; RNA interference (RNAi); antimicrobial peptides; soluble lectins; and metabolite-mediated inhibition of microbial replication**

Degenerative mechanisms

The second class of constitutive innate immune mechanisms functions through the **degradation of danger molecules and elimination of unwanted cells**. This class of mechanisms includes **autophagy, phagocytosis, proteasomal degradation and nucleases**. Collectively, degenerative programmes function to continually limit danger signals, allowing for the rapid elimination of unwanted molecules without the activation of energy-consuming amplificative induced immune responses

Pattern-recognition receptors (PRRs) are evolutionarily conserved germline-encoded receptors, which, although structurally different, share a common feature of detecting pathogen-associated molecular patterns (PAMPs)

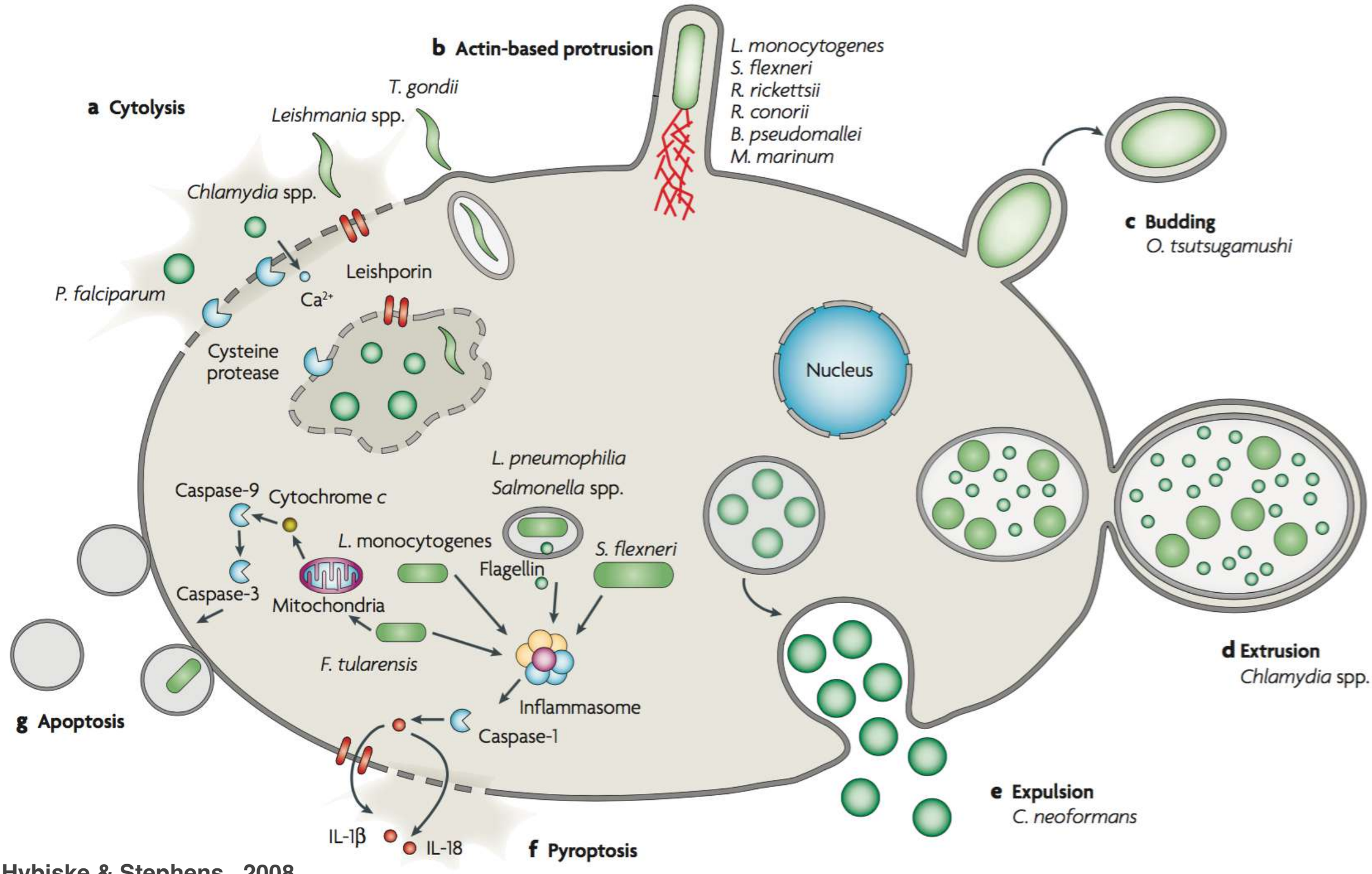
Toll-like receptors (TLRs) Ten TLRs have been identified in humans and twelve in mice.
TLRs are type I **transmembrane glycoproteins that localize to either the plasma membrane** (in the case of TLR1–TLR6, TLR10 and TLR11) or the **endosomal membrane** (in the case of TLR3, TLR7 and TLR9, for example). Ligands for TLRs include bacterial **lipoproteins and lipopeptides** (for TLR2), **double-stranded RNA** (for TLR3), l**ipopolysaccharide** (for TLR4), **flagellin** (for TLR5), **single-stranded RNA** (for TLR7), CpG **DNA** (for TLR9)

NOD-like receptors (NLRs) NLRs constitute a large family of cytosolic proteins.
The first family members to be discovered — nucleotide-binding oligomerization domain protein 1 (NOD1) and NOD2 — recognize **bacterial peptidoglycan** fragments and activate nuclear factor-κB (NF-κB) signalling

RIG-I-like receptors (RLRs).
There are three known RLRs: retinoic acid-inducible gene I (RIG-I), melanoma differentiationassociated gene 5 (MDA5) and LGP2. RLRs are expressed in the **cytosol and sense nucleic acids, such as viral RNA**

C-type lectin receptors (CLRs).
The CLRs are a large family of proteins that possess one or more C-type lectin domains and one or more immunoreceptor tyrosine-based activation motifs (ITAMs). They recognize a wide range of **carbohydrate ligands** (and probably also non-carbohydrate ligands)

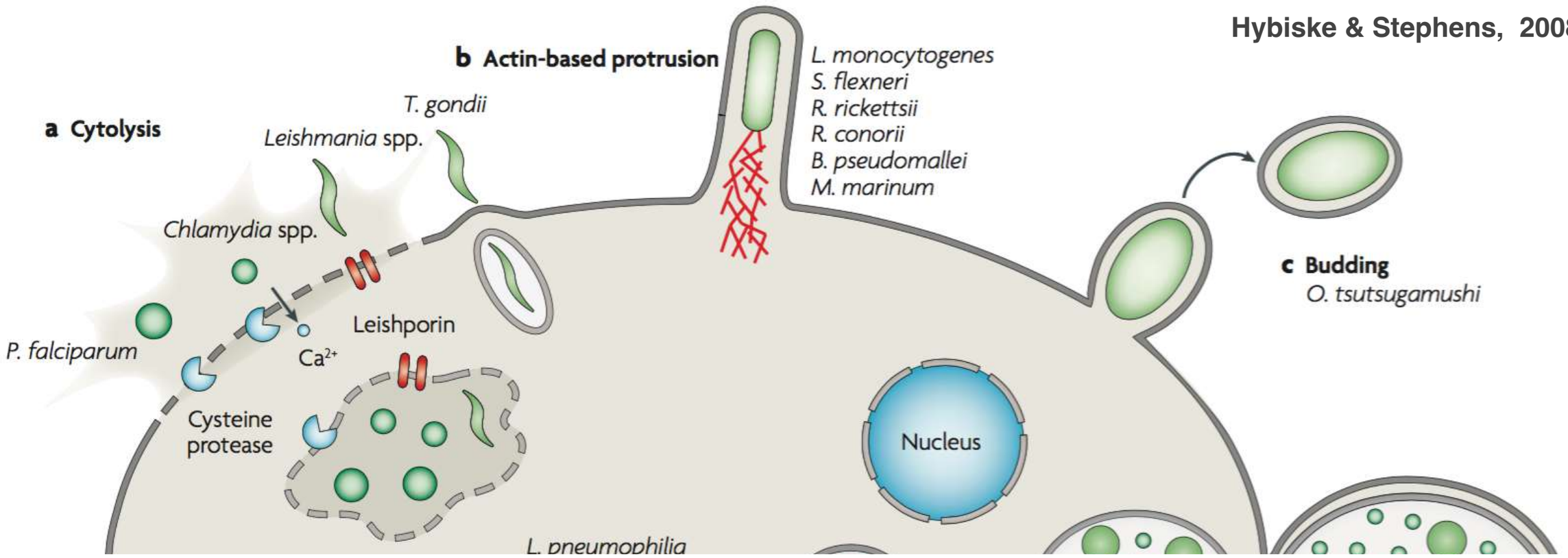
Strategies and mechanisms used by intracellular pathogens to exit host cells



Hybiske & Stephens, 2008

Cytolysis and Actin-based protrusion

Hybiske & Stephens, 2008



a | **The cytolysis, and destructive and sequential rupture, of the vacuole and cell membranes**. Putative mechanisms include proteases (*Plasmodium falciparum* and *Chlamydia* spp.), pore-forming proteins (PFPs) (*Leishmania* spp.) and the unique mechanism of *Toxoplasma gondii*.

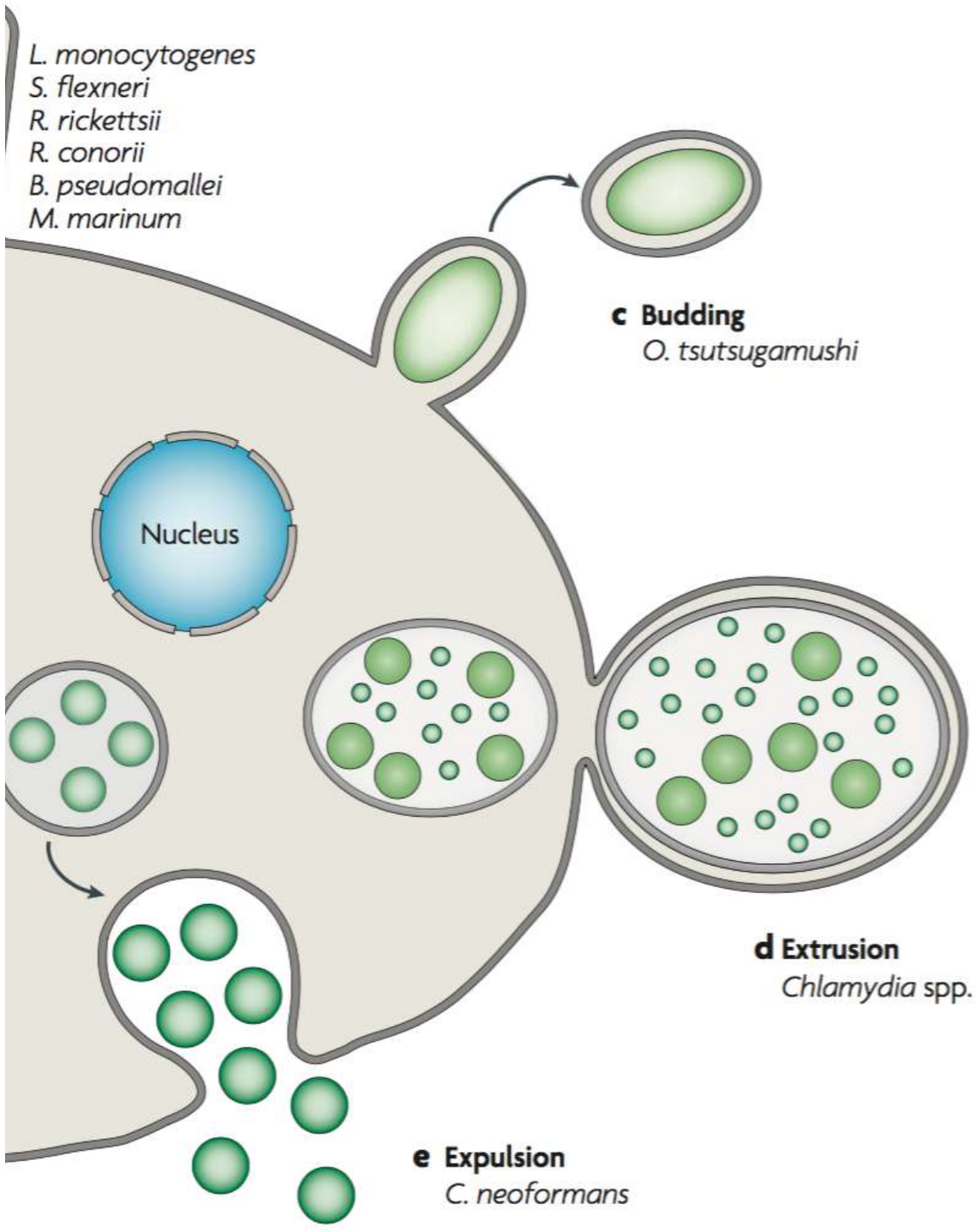
b | **Actin-based protrusion**, which is exploited by *Listeria monocytogenes, Shigella flexneri, Rickettsia rickettsii, Rickettsia conorii, Burkholderia pseudomallei* and *Mycobacterium marinum*, results in a single bacterium that **uses the force that is generated by actin polymerization to protrude** from the cell membrane and force engulfment into a neighbouring cell.

Budding, Extrusion and Phagosomal expulsion

c | The **budding** of *Orientia tsutsugamushi*, in which a single bacterium is encased by plasma membrane.

d | The **extrusion** of *Chlamydia* spp., in which the large *Chlamydia*-containing **vacuole** pinches off and extrudes out of the cell; the extruded vacuole is encased by cytosol and plasma membrane.

e | The p**hagosomal expulsion** of *Cryptococcus neoformans*, in which the large vacuole fuses with the plasma membrane by an undefined exocytic process.

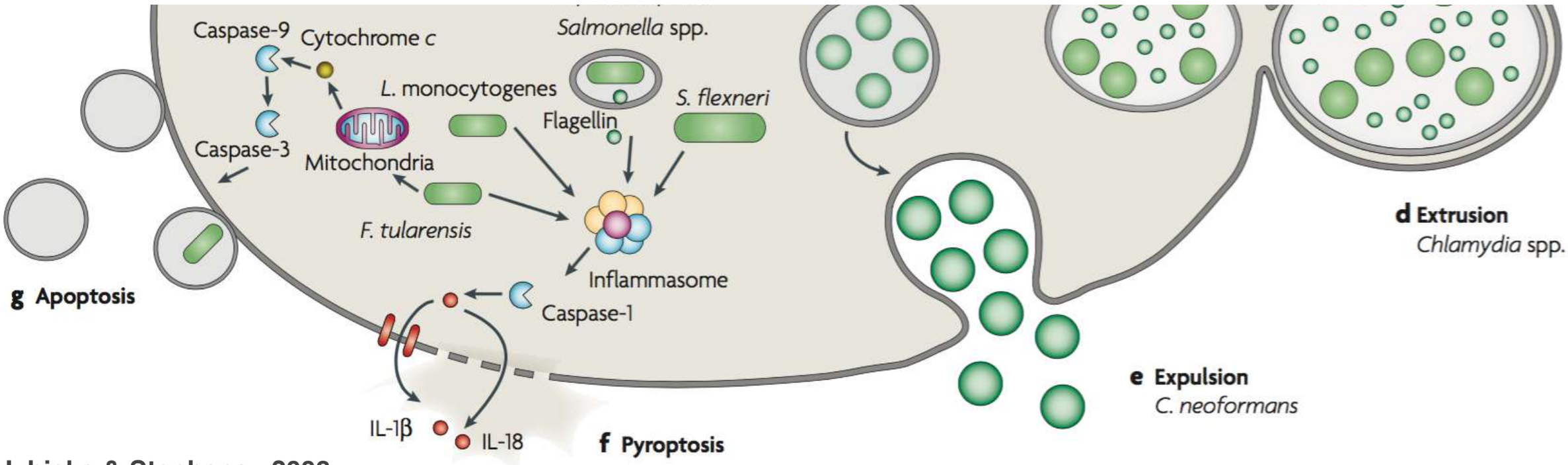


Hybiske & Stephens, 2008

Pyroptosis and Apoptosis

f | Proinflammatory pyroptosis is defined by the sensing of bacterial molecules (flagellin of *Legionella pneumophila* and *Salmonella* spp. and unknown molecules of *S. flexneri*, *L. monocytogenes* and *Francisella tularensis*) through the host **inflammasome**. The inflammasome proteolytically activates caspase-1, which leads to interleukin (IL)-1β and IL-18 activation and secretion. Cytokine secretion occurs initially through a caspase-1-dependent pore, and is then released upon necrotic cell lysis.

g | **Apoptosis** is induced by *F. tularensis* using the intrinsic pathway of activation — cytochrome *c* release from mitochondria and activation of the initiator caspase-9 and the effector caspase-3. The bacterial molecule (or molecules) that is responsible for apoptotic induction is unknown.



Hybiske & Stephens, 2008

Microbes and Humans

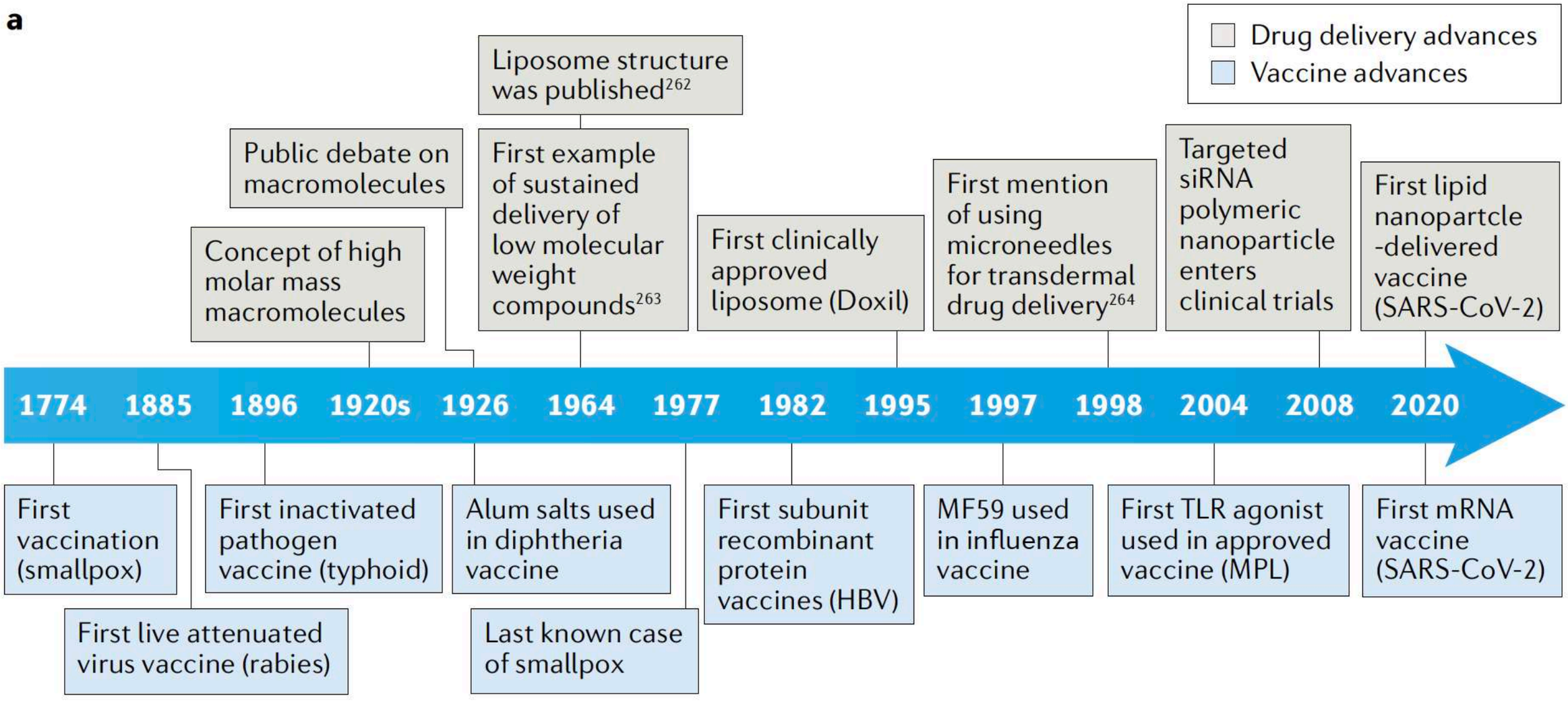
- Providing nutrients
- Fighting off microbial pathogens
- Maintaining the Human ecosystem functioning = healthy
- Training immune system to recognise the commensals from the pathogens (failure—> sepsis and microbial invasion/disease)
- Training immune system to recognise self from non self (failure—> autoimmune and allergic diseases)

Vaccine

A vaccine is a biological product that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen

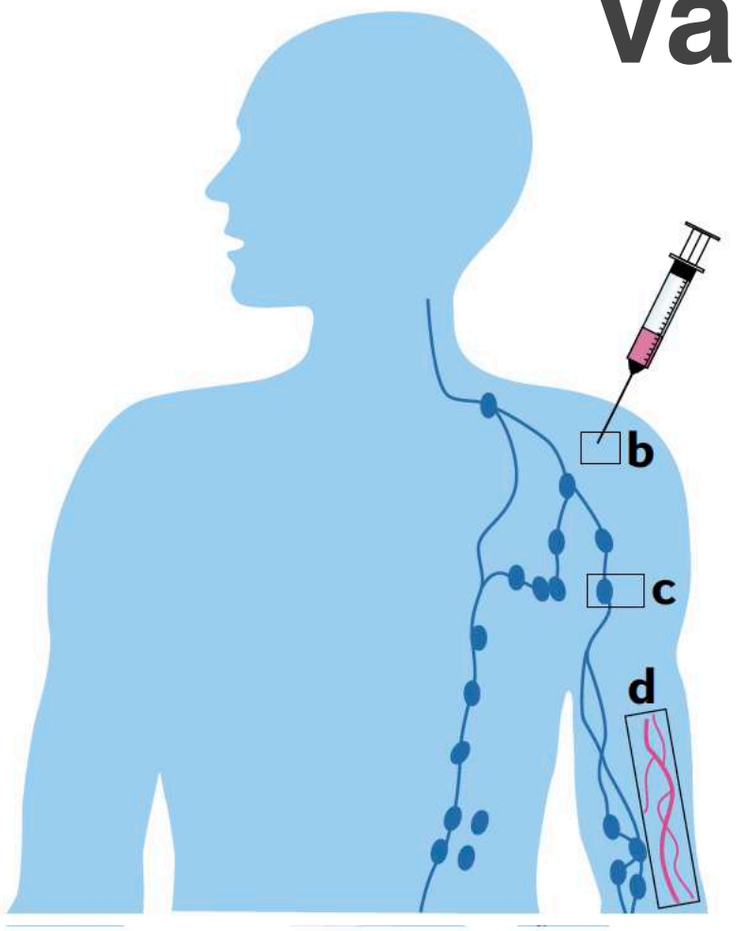
To achieve this, the vaccine must contain antigens that are either derived from the pathogen or produced synthetically to represent components of the pathogen

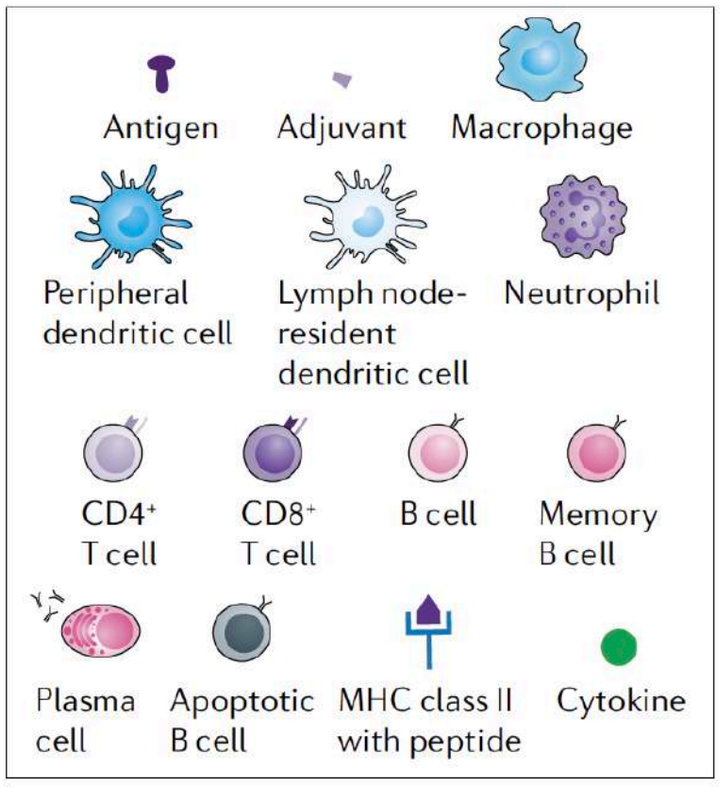
Vaccine timeline

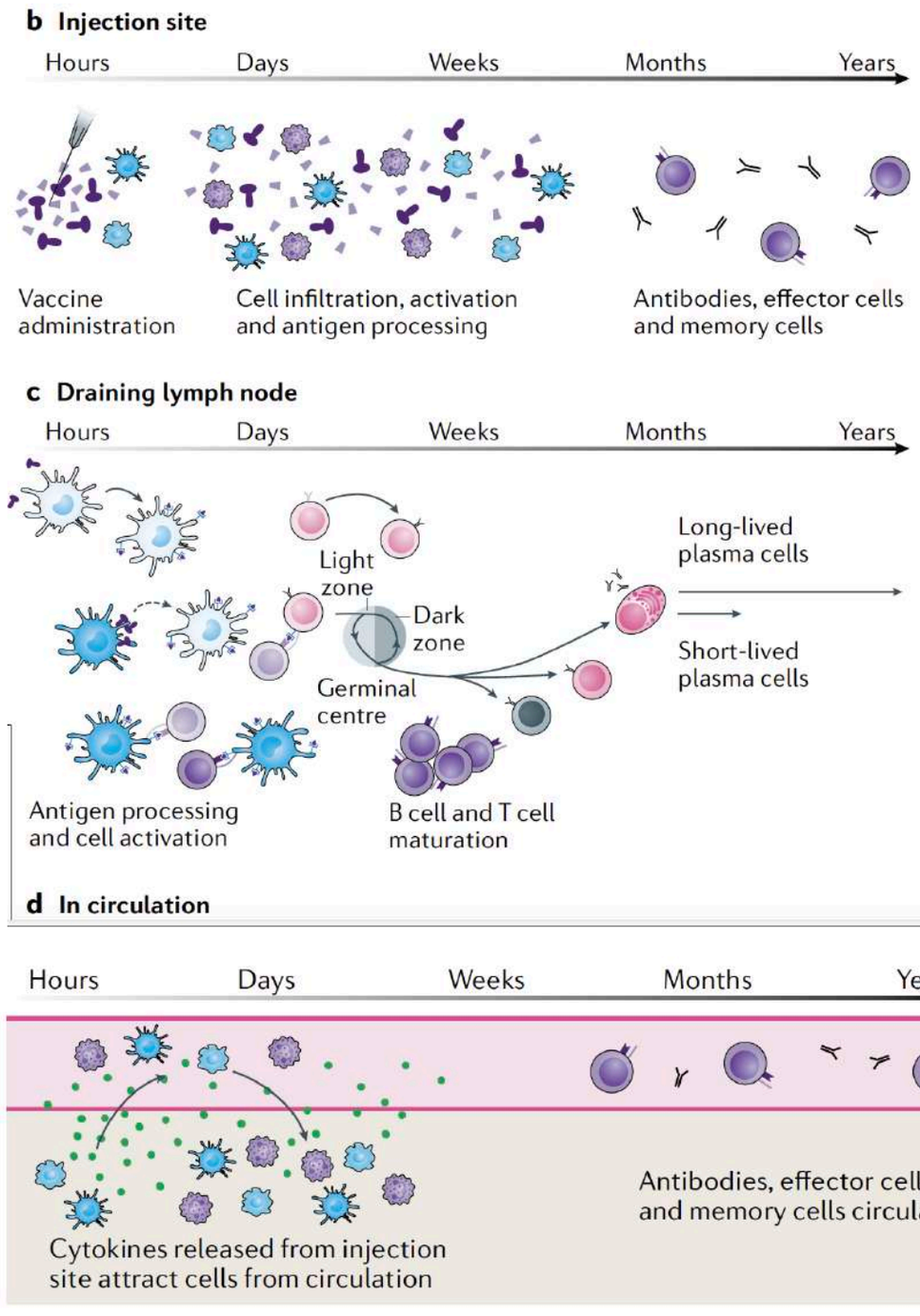


Roth et al., 2022

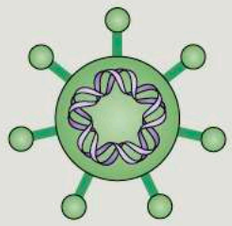
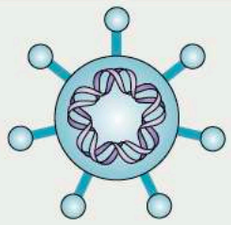
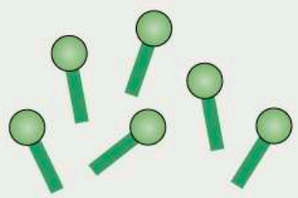
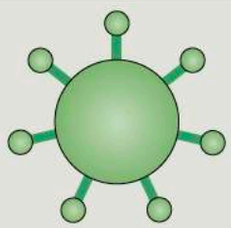
Vaccine immune response





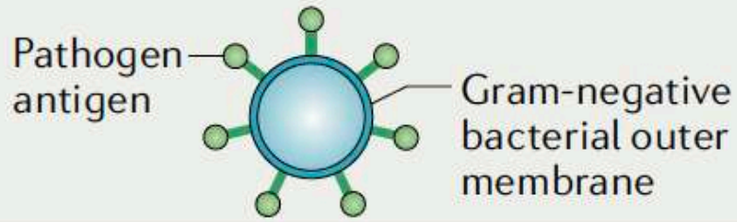
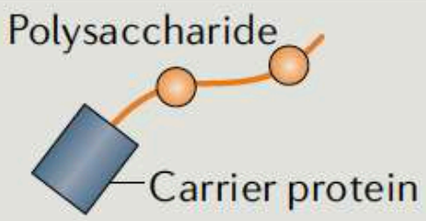
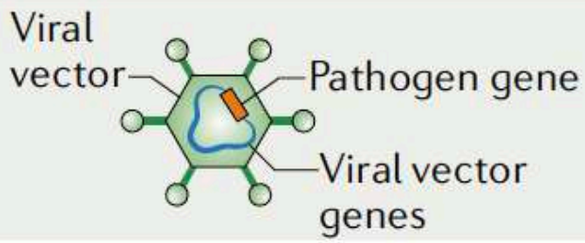
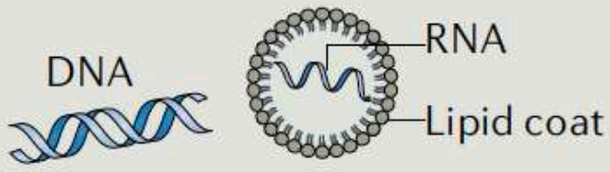
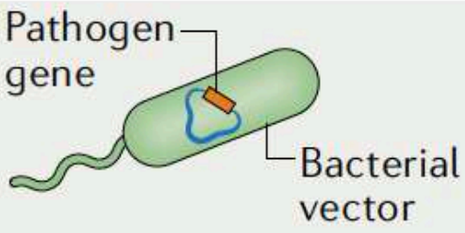
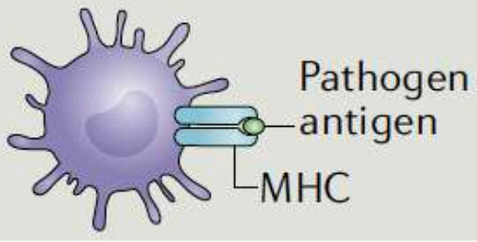


Roth et al., 2022

Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle		Human papillomavirus	1986 (hepatitis B)

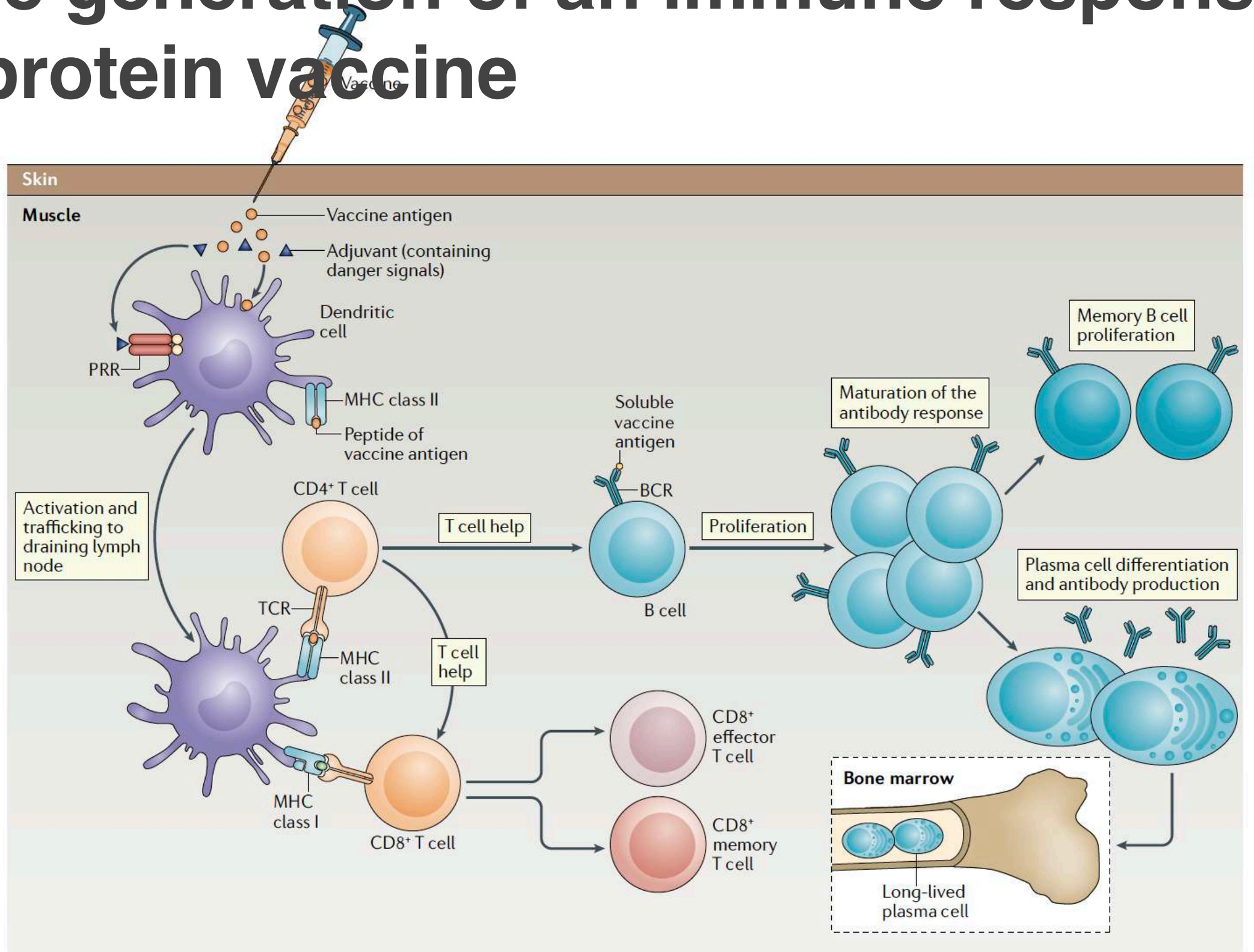
Pollard & Bijker, 2021

BCG, Mycobacterium bovis bacillus Calmette–Guérin.

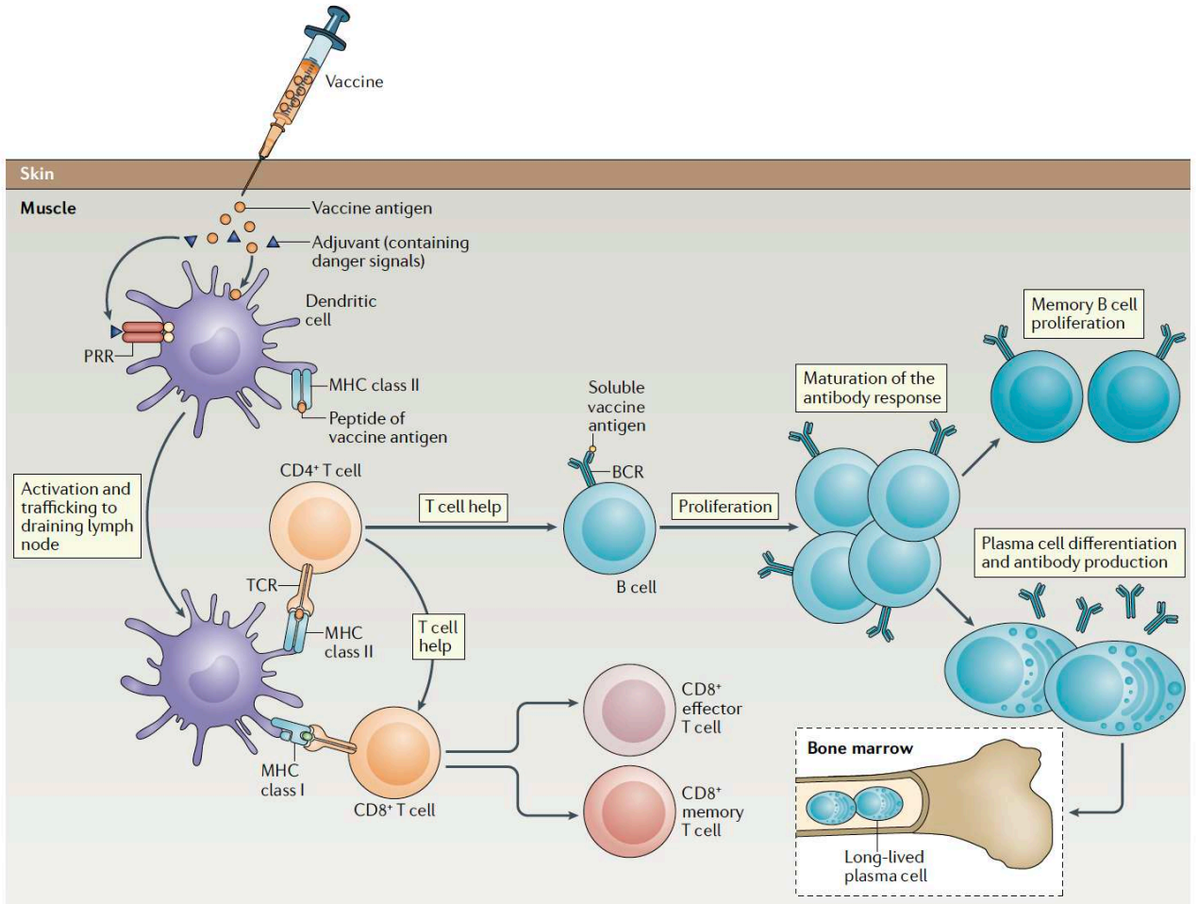
Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored		Experimental	–
Antigen-presenting cell		Experimental	–

Pollard & Bijker, 2021

The generation of an immune response to a protein vaccine



Pollard & Bijker, 2021



Pollard & Bijker, 2021

The vaccine is injected into muscle and the protein antigen is taken up by dendritic cells, which are activated through pattern recognition receptors (PRRs) by danger signals in the adjuvant, and then trafficked to the draining lymph node

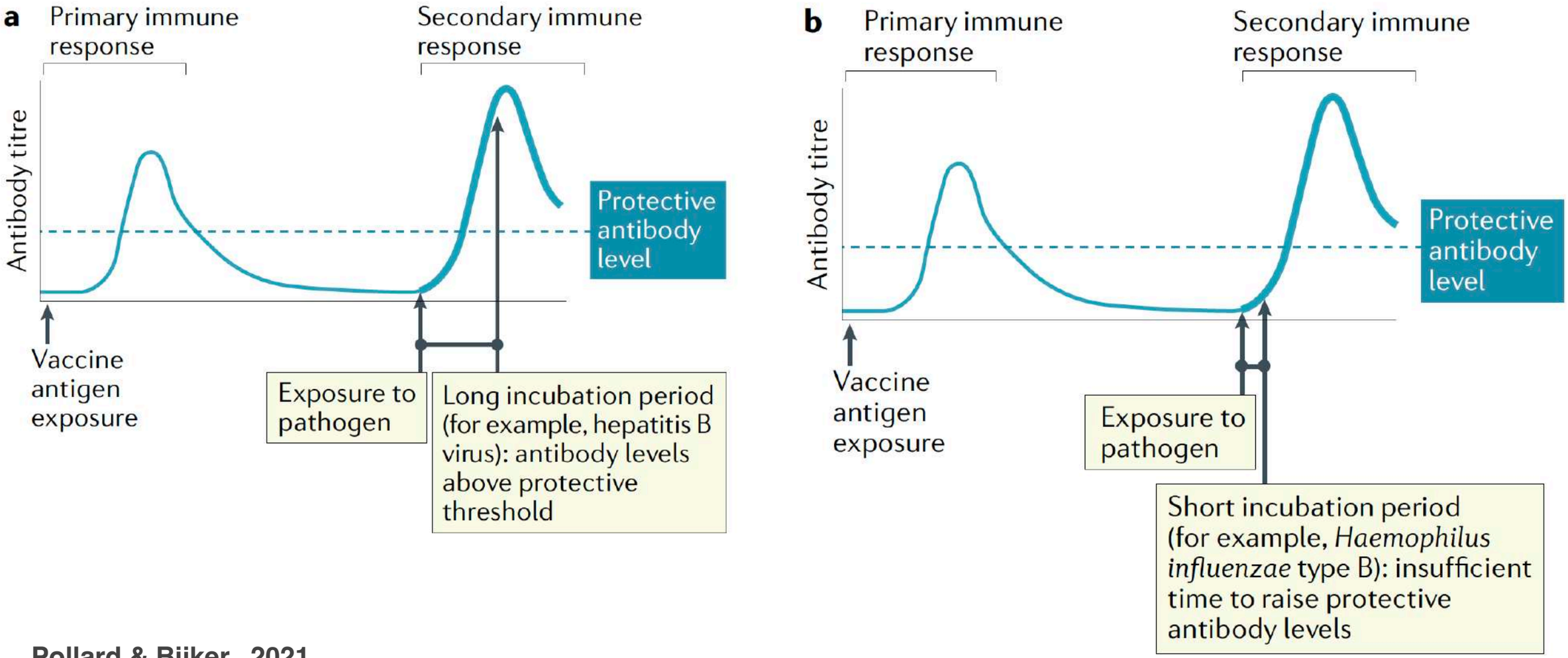
Here, the presentation of peptides of the vaccine protein antigen by MHC molecules on the dendritic cell activates T cells through their T cell receptor (TCR)

In combination with signalling (by soluble antigen) through the B cell receptor (BCR), the T cells drive B cell development in the lymph node. Here, the T cell-dependent B cell development results in maturation of the antibody response to increase antibody affinity and induce different antibody isotypes

The production of short-lived plasma cells, which actively secrete antibodies specific for the vaccine protein, produces a rapid rise in serum antibody levels over the next 2 weeks

Memory B cells are also produced, which mediate immune memory. Long-lived plasma cells that can continue to produce antibodies for decades travel to reside in bone marrow niches. CD8+ memory T cells can proliferate rapidly when they encounter a pathogen, and CD8+ effector T cells are important for the elimination of infected cells.

Immune memory is an important feature of vaccine-induced protection, I

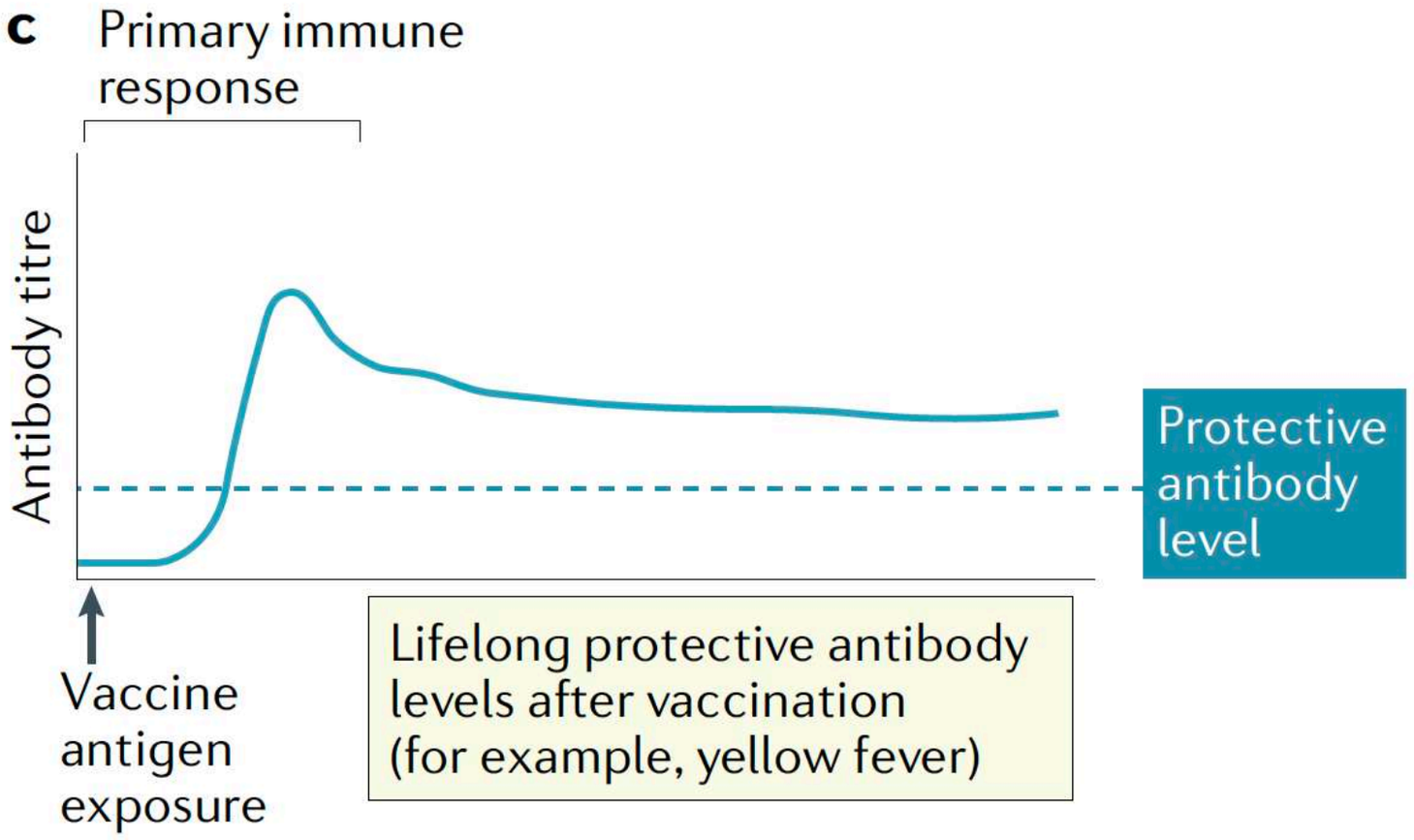


Pollard & Bijker, 2021

Antibody levels in the circulation wane after primary vaccination, often to a level below that required for protection

Whether immune memory can protect against a future pathogen encounter depends on the incubation time of the infection, the quality of the memory response and the level of antibodies induced by memory B cells

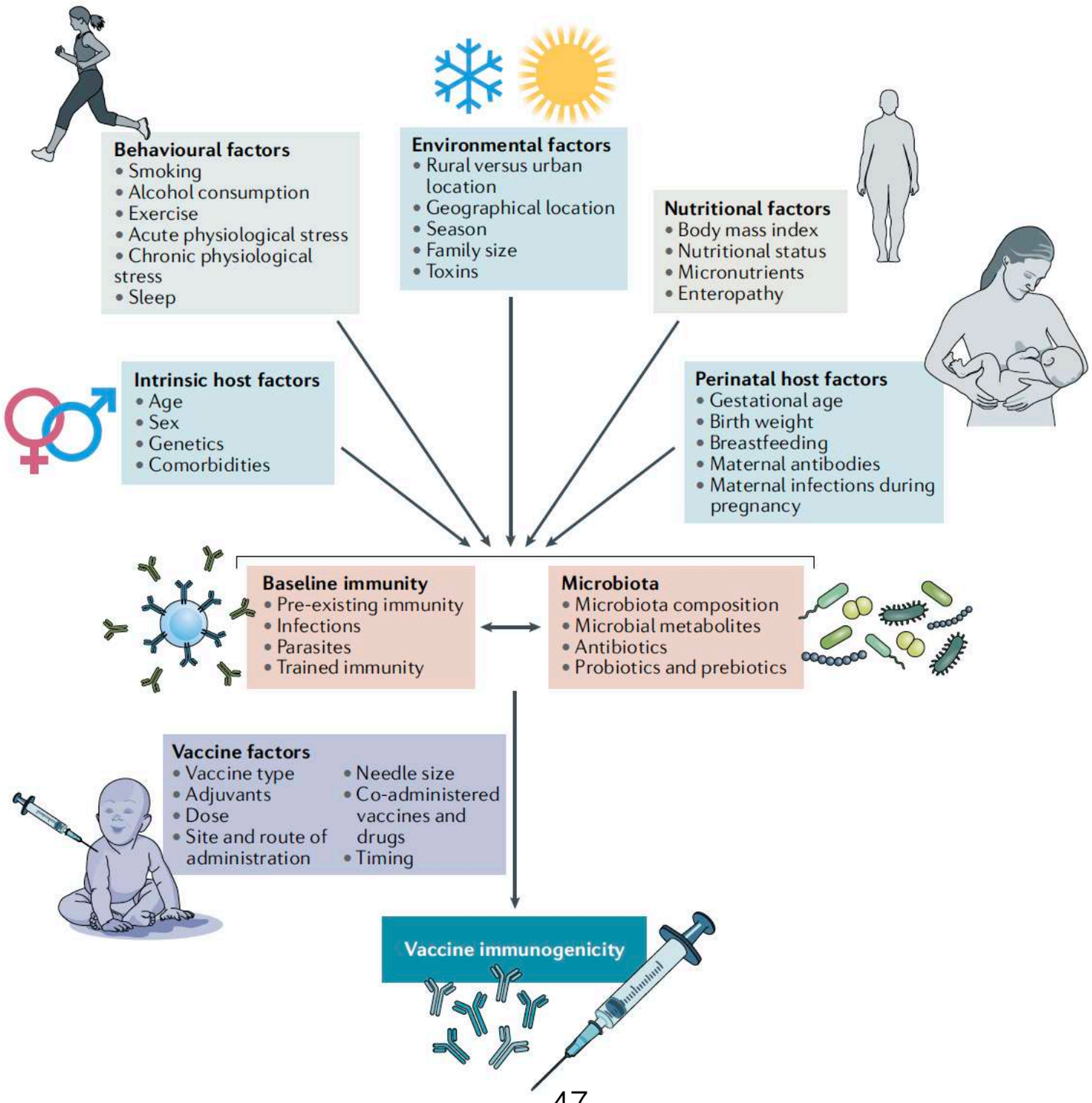
Immune memory is an important feature of vaccine-induced protection, II



Pollard & Bijker, 2021

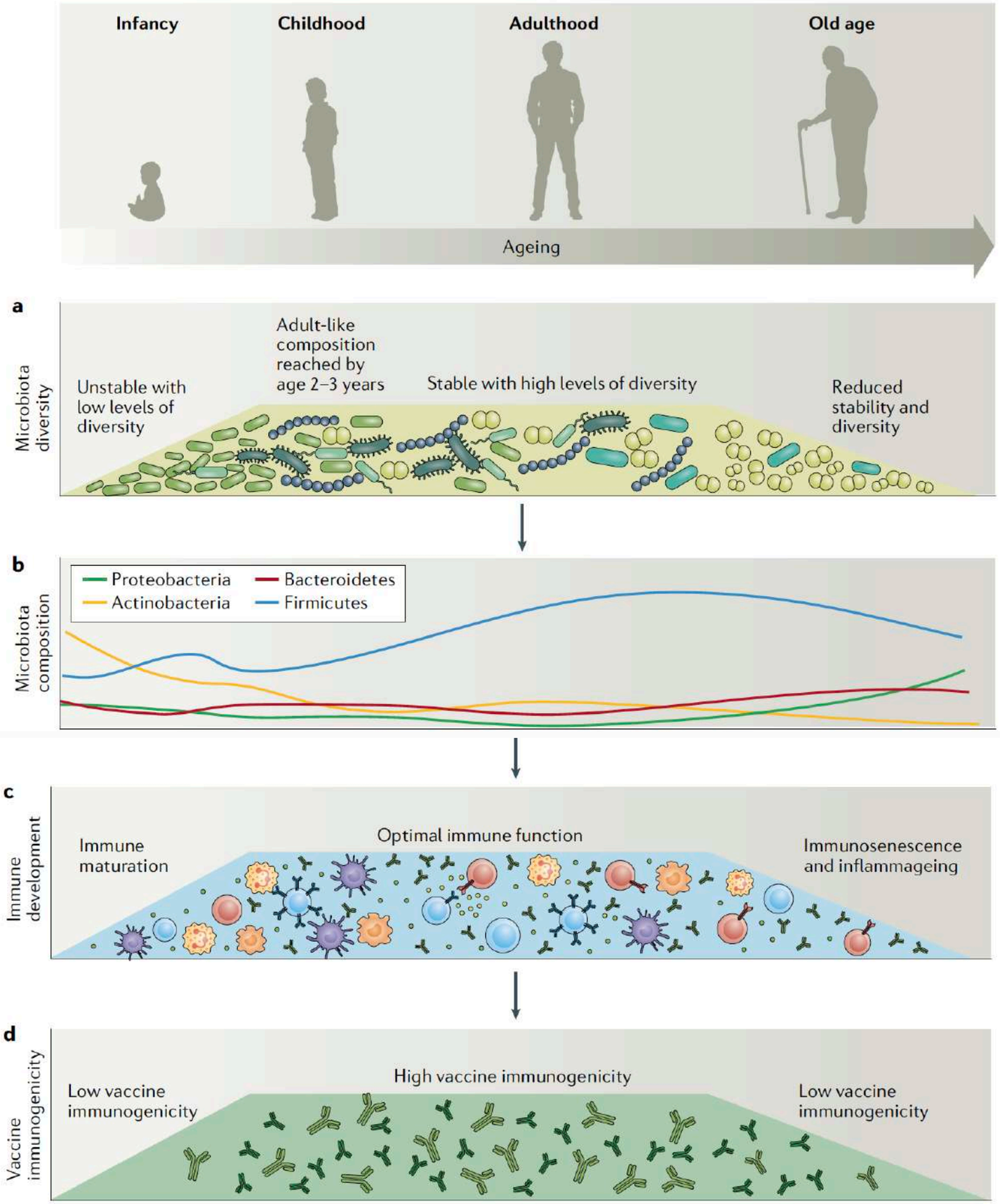
Life long immunity

Factors with the potential to influence vaccine immunogenicity and/or efficacy

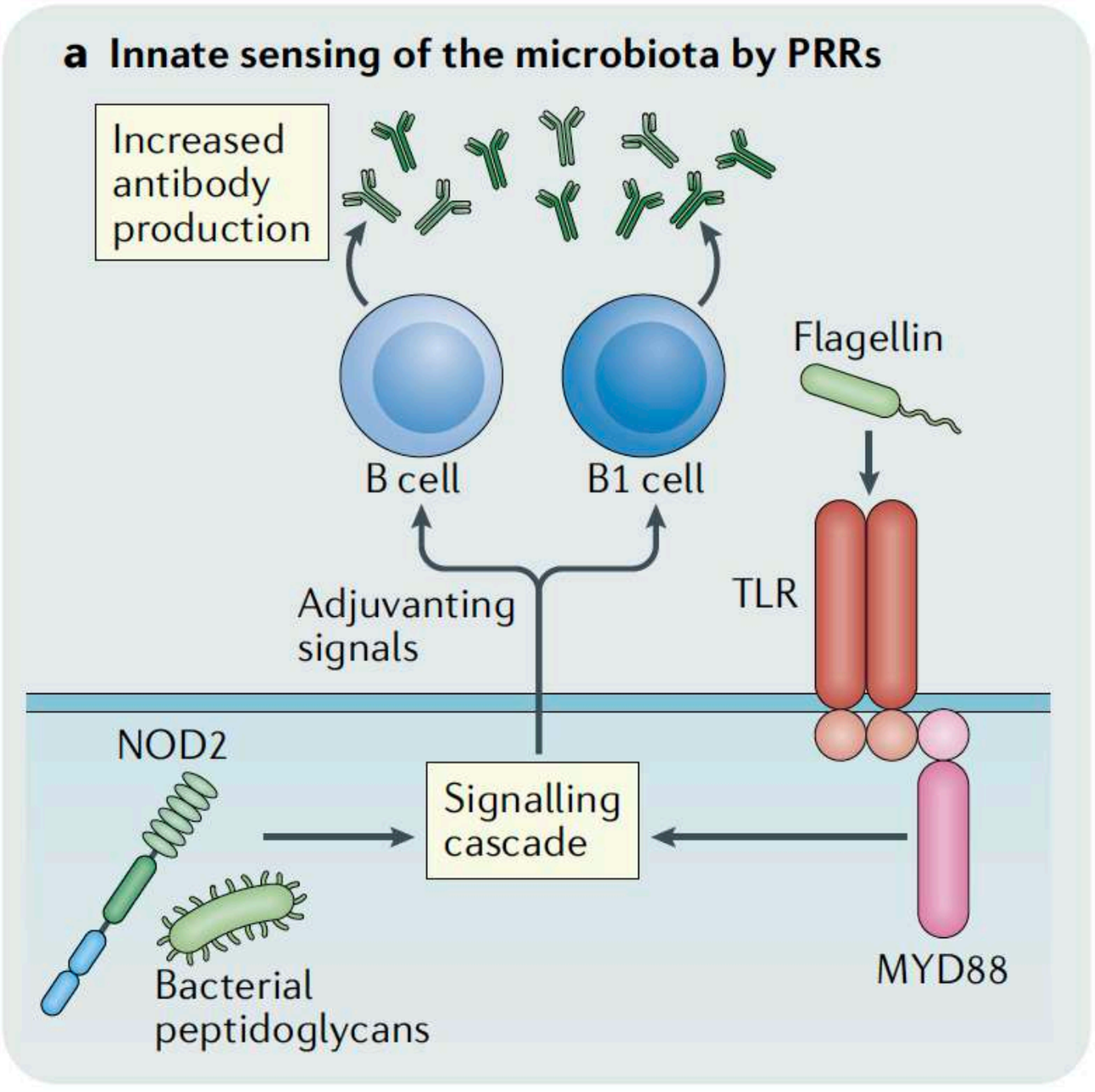


Lynn et al., 2022

Differences in the gut microbiota of infants and the elderly compared with that of young adults correlate with altered immune status and suboptimal vaccine immunogenicity



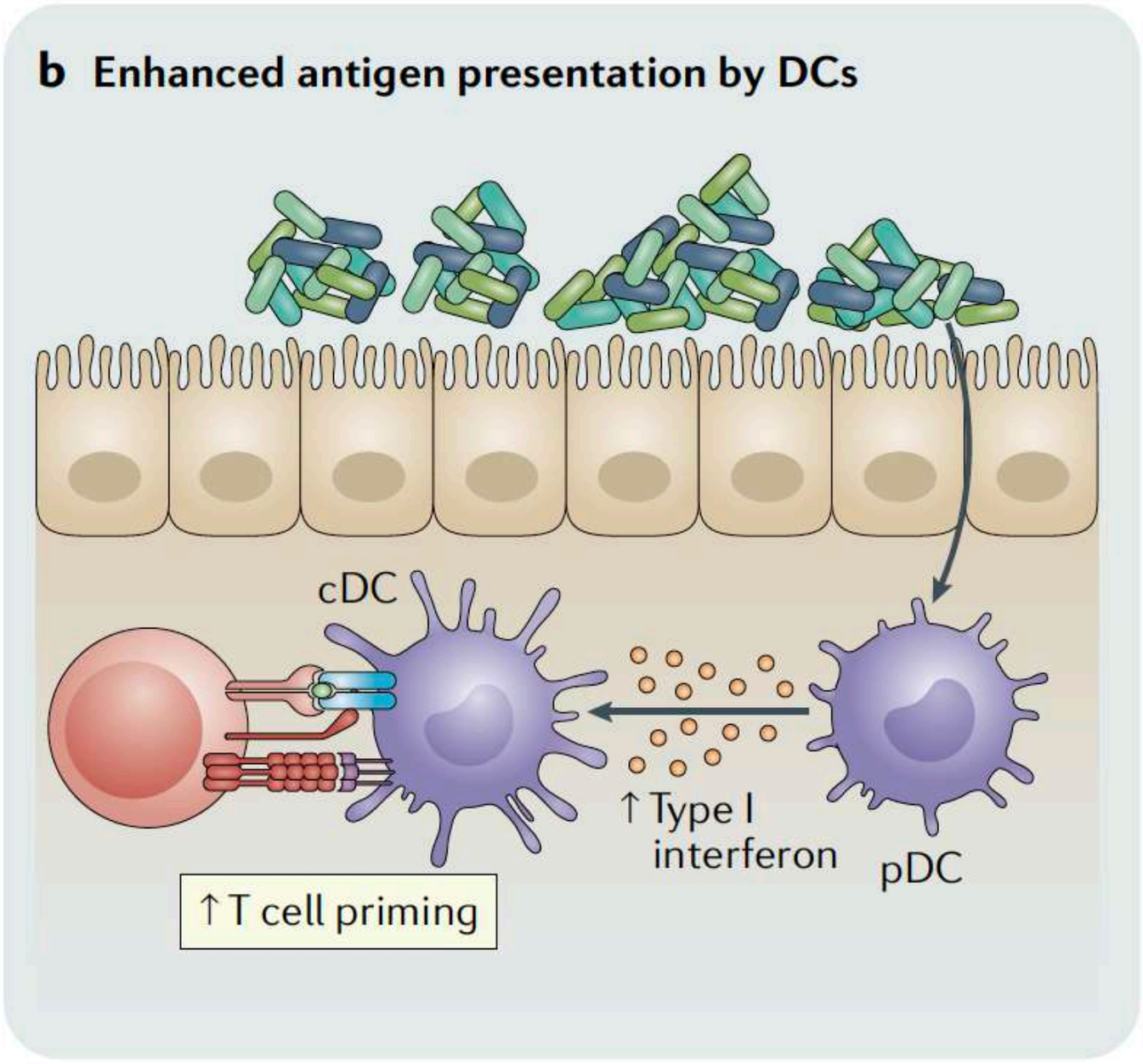
Lynn et al., 2022



Immunomodulatory molecules produced by the microbiota, such as **flagellin and peptidoglycan**, have been shown in animal models to **modulate vaccine responses by providing natural adjuvants** that are sensed by pattern recognition receptors (PRs), such as Toll-like receptors (TLRs) and NOD2, expressed by antigen-presenting cells.

Other **immunomodulatory** molecules, such as **lipopolysaccharide**, may also similarly modulate responses. PRs expressed by T cells and B cells may also sense these molecules directly.

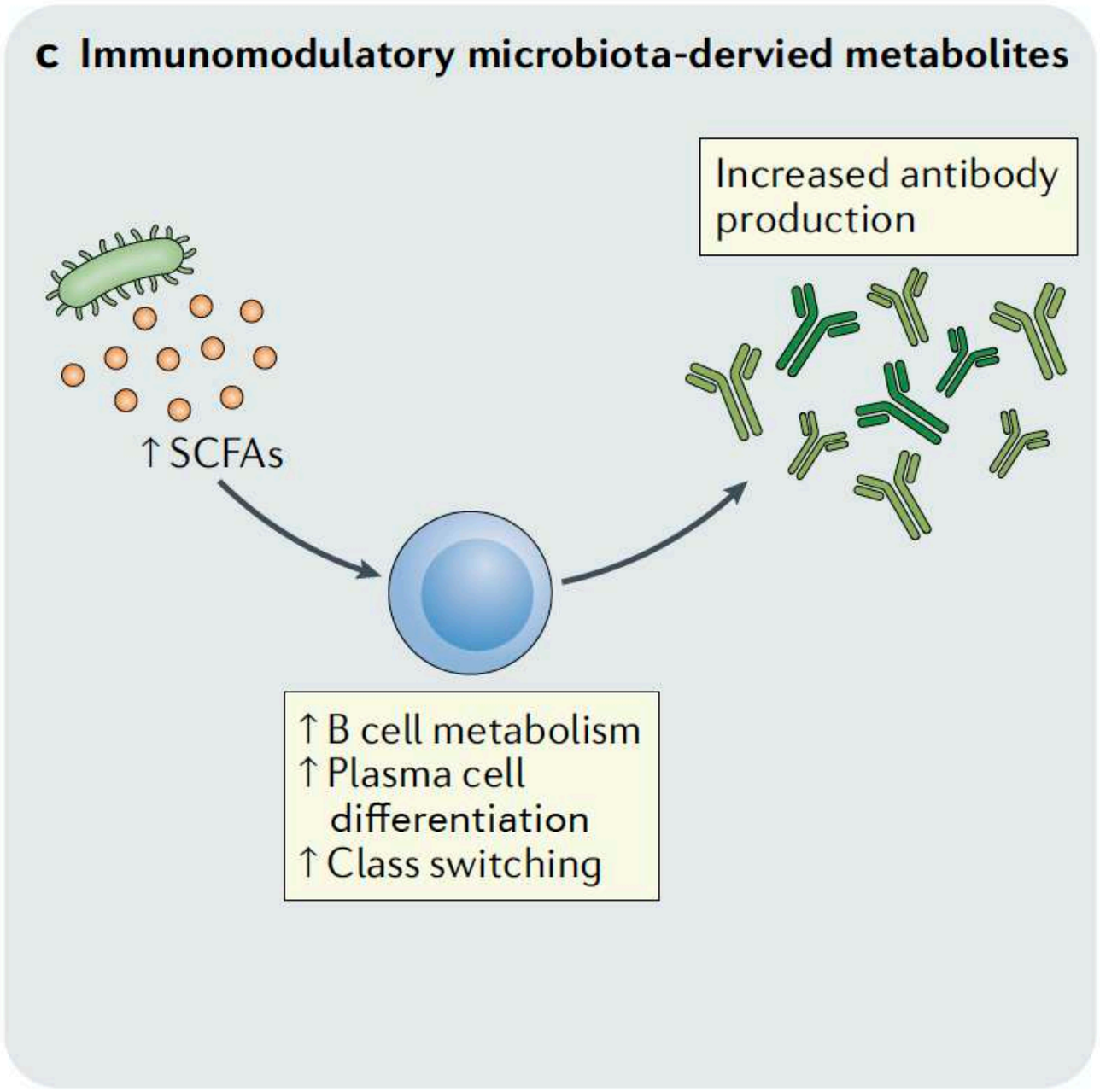
Lynn et al., 2022



Dendritic cells (DCs) have a crucial role in immune responses to vaccination by presenting vaccine antigens to T cells and secreting immunomodulatory cytokines.

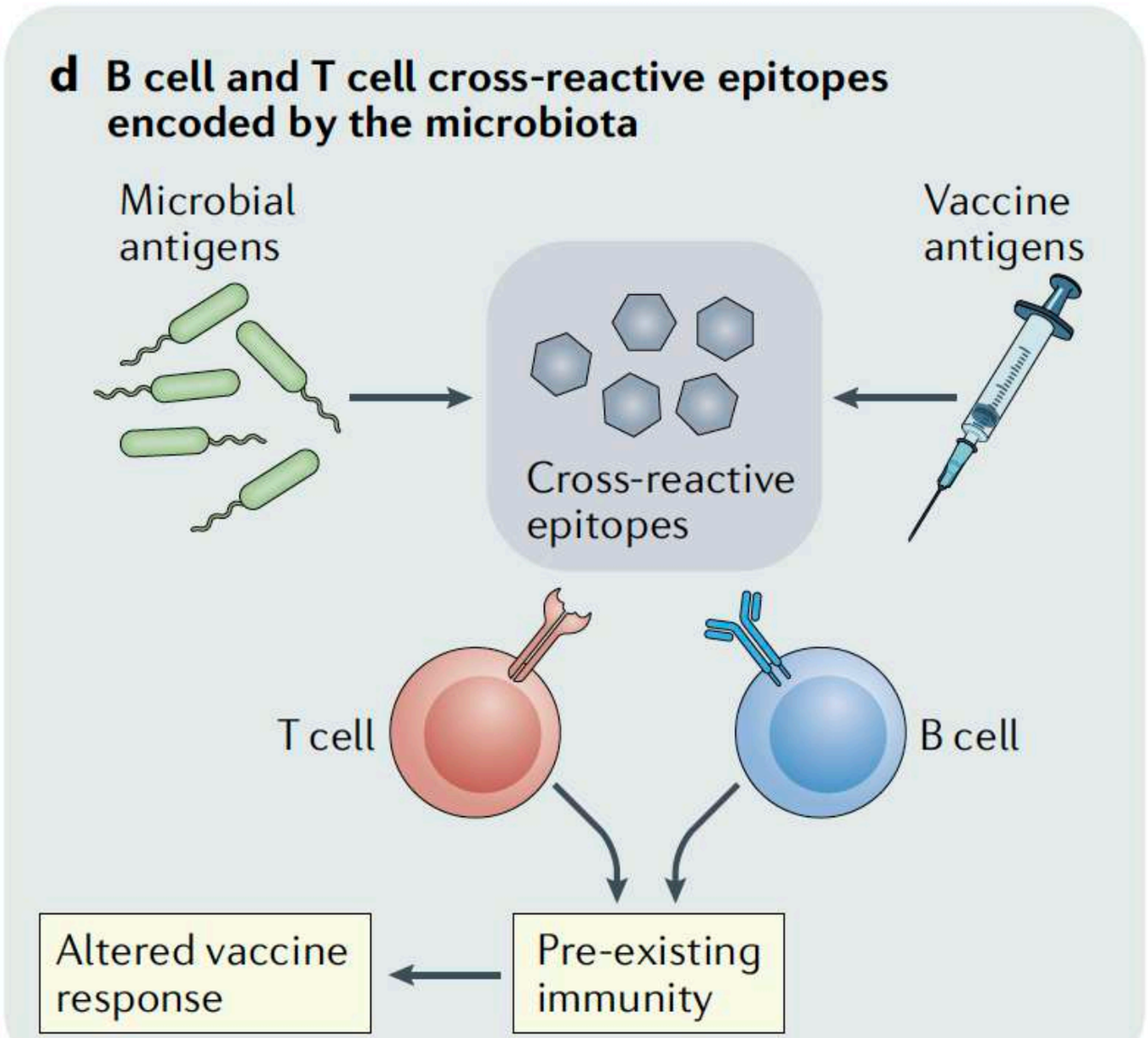
The microbiota regulates the production of type I interferons by plasmacytoid DCs (pDCs), which in turn instruct a specific metabolic and epigenomic state in conventional DCs (cDCs) that enhances T cell priming.

Lynn et al., 2022



Immunomodulatory metabolites produced by the microbiota, such as short-chain fatty acids (SCFAs), can enhance B cell metabolism to support the energy demands of antibody production and can increase the expression of genes involved in plasma cell differentiation and class switching, potentially altering responses to vaccination.

Lynn et al., 2022

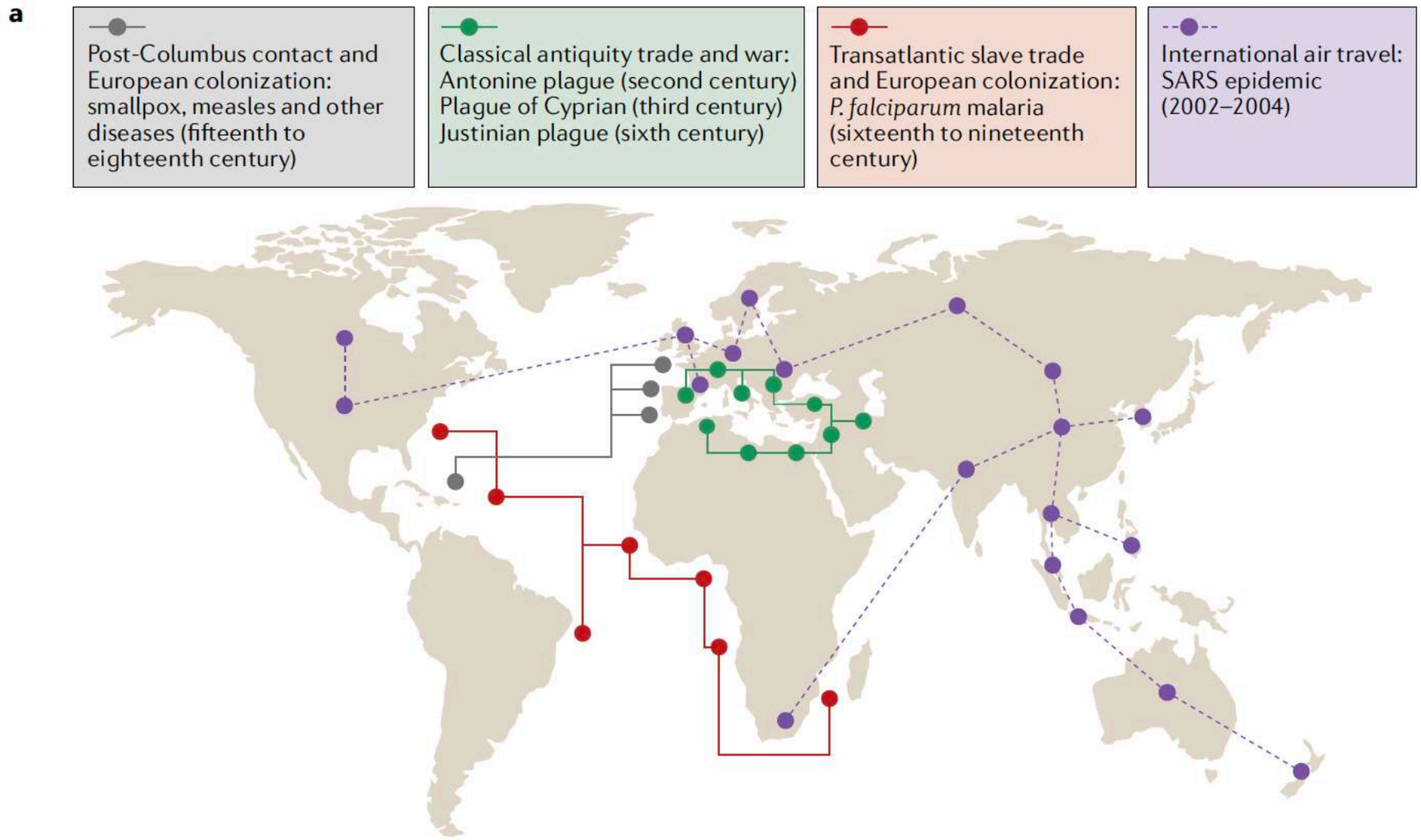


Increasing data suggest that the **microbiota can encode epitopes that are cross-reactive with pathogen-encoded or vaccine-encoded epitopes**. The presence of cross-reactive
B cells or T cells could potentially alter the responses to vaccination.

Lynn et al., 2022

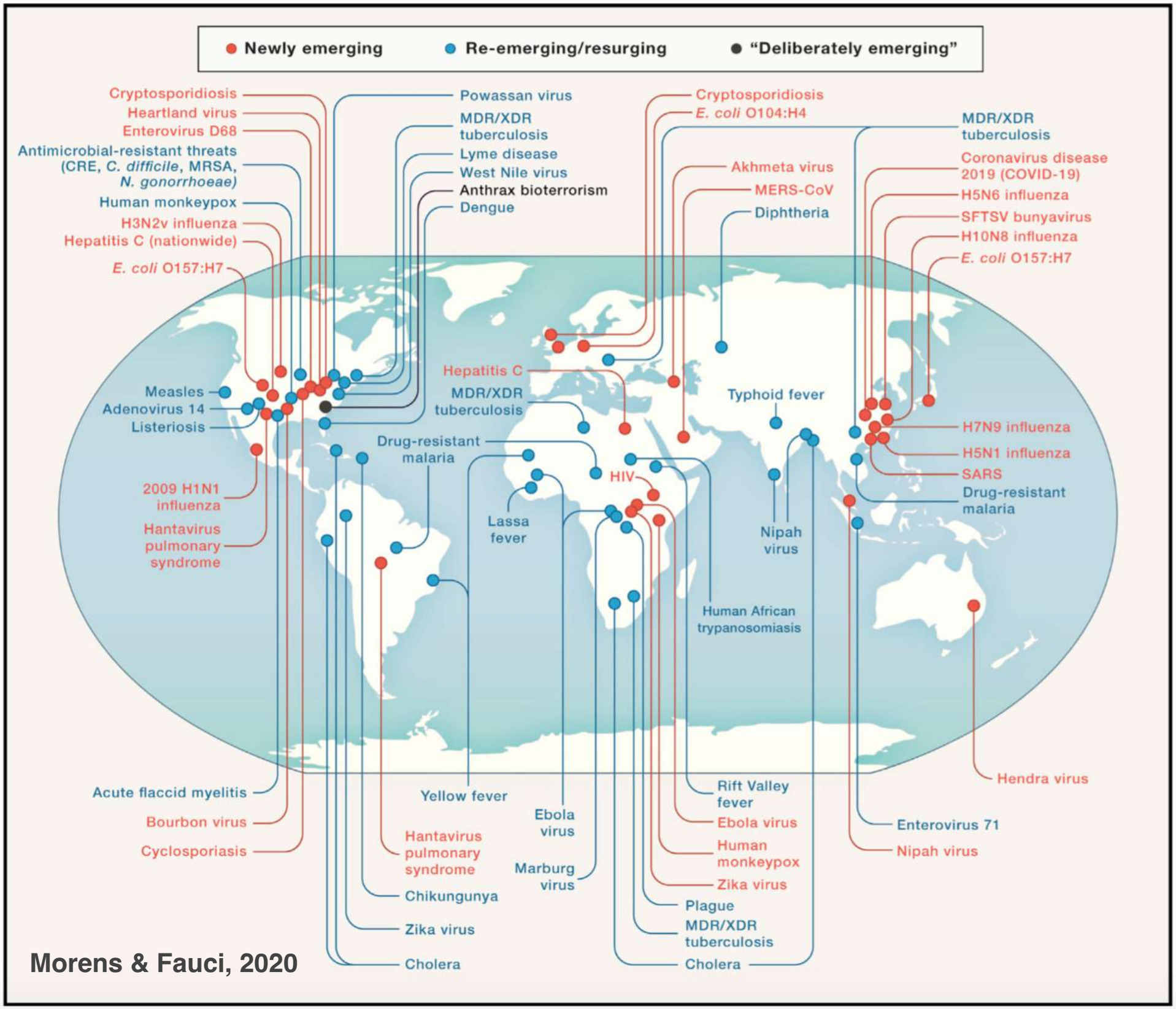
OneHealth

Human connectivity and infectious disease outbreaks in premodern and modern times



Backer et al., 2022

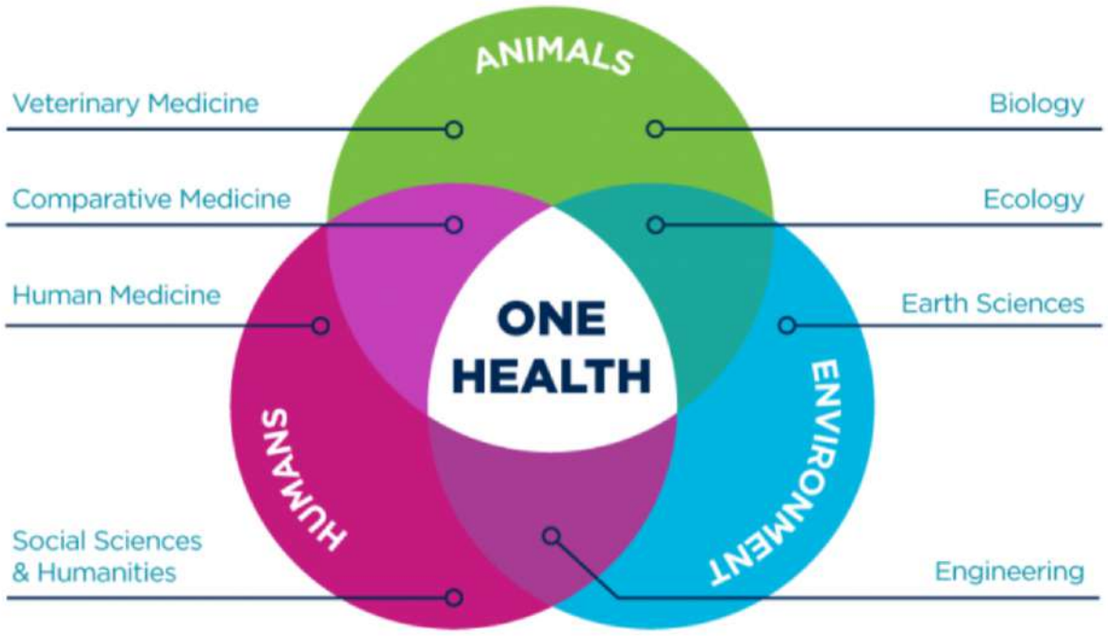
Infectious disease from 1981 to 2020

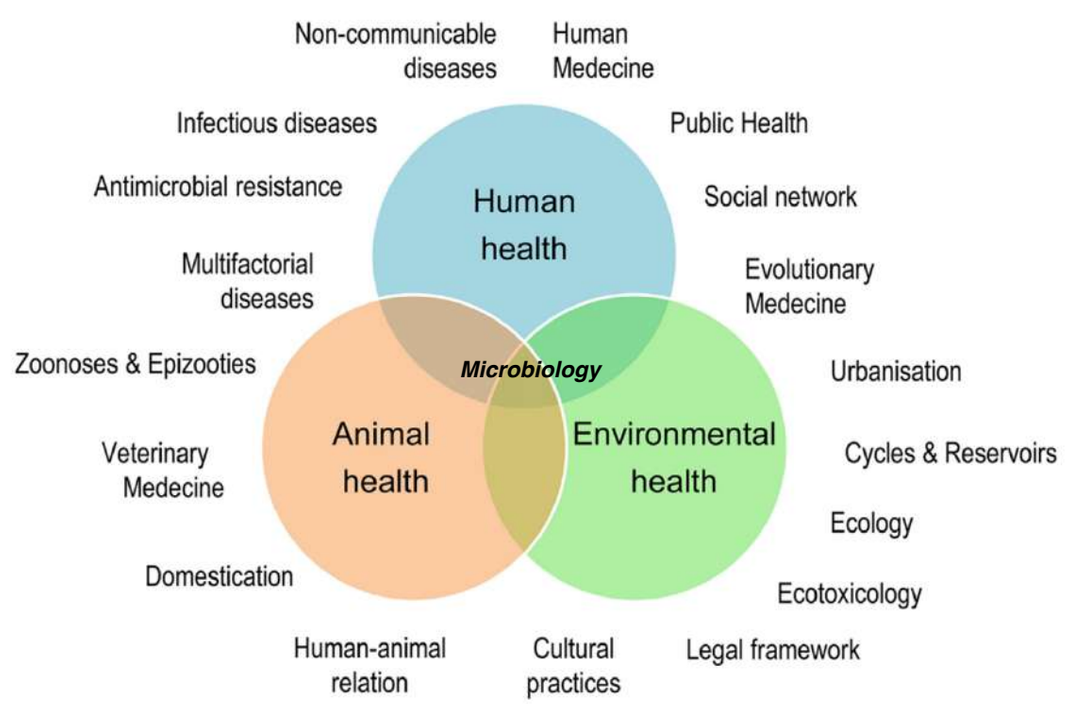


Morens & Fauci, 2020

One Health: approach to designing and implementing programs, policies, legislation and research in which multiple sectors communicate and work together **to achieve better public health outcomes**

Holistic approach where interactions matter





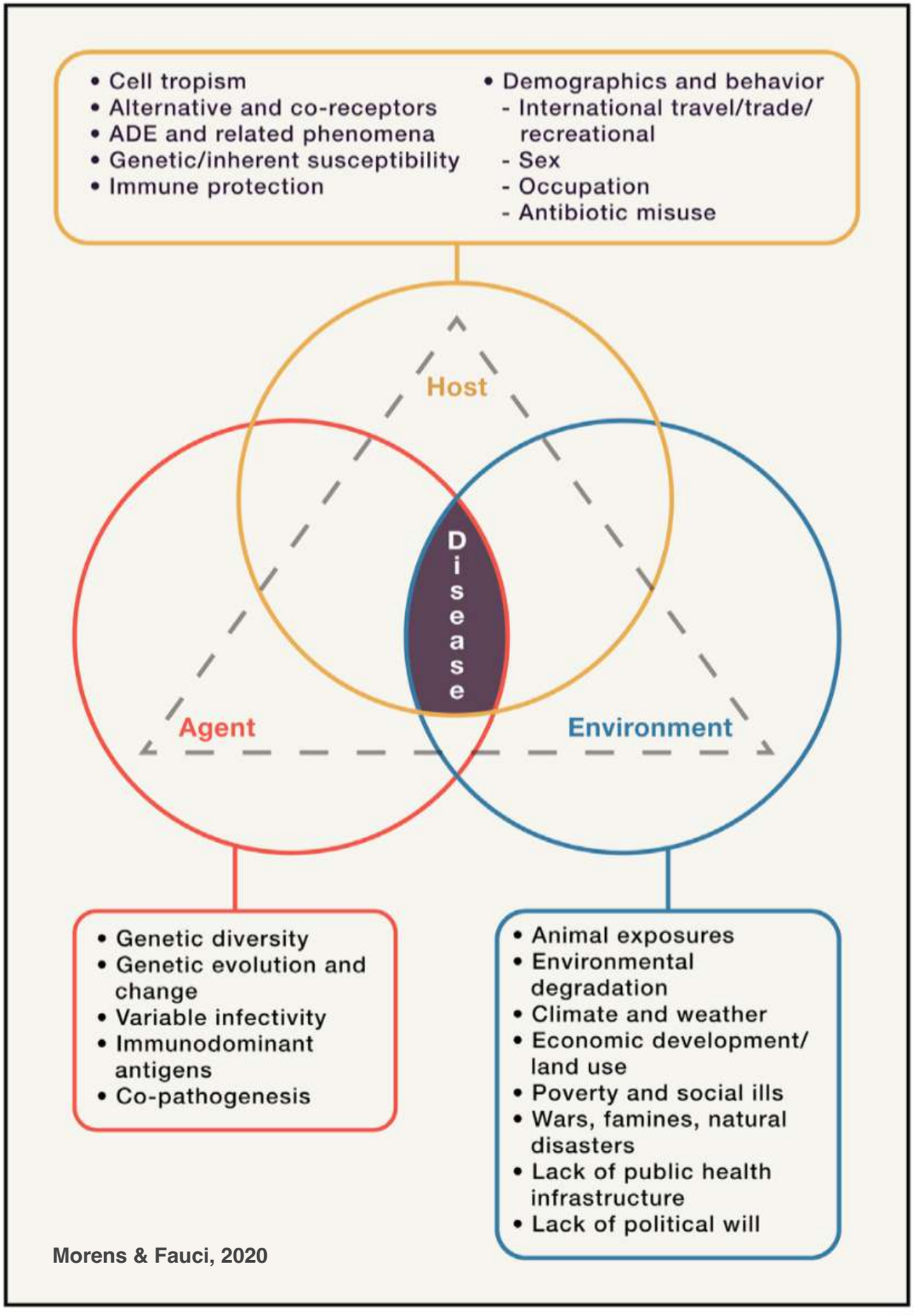
Destoumieux-Garzon et al., 2018

Original author not found

One Health issues include **zoonotic diseases, antimicrobial resistance**, food safety and food security, vector-borne diseases, environmental contamination, and other health threats **shared** by people, animals, and the environment

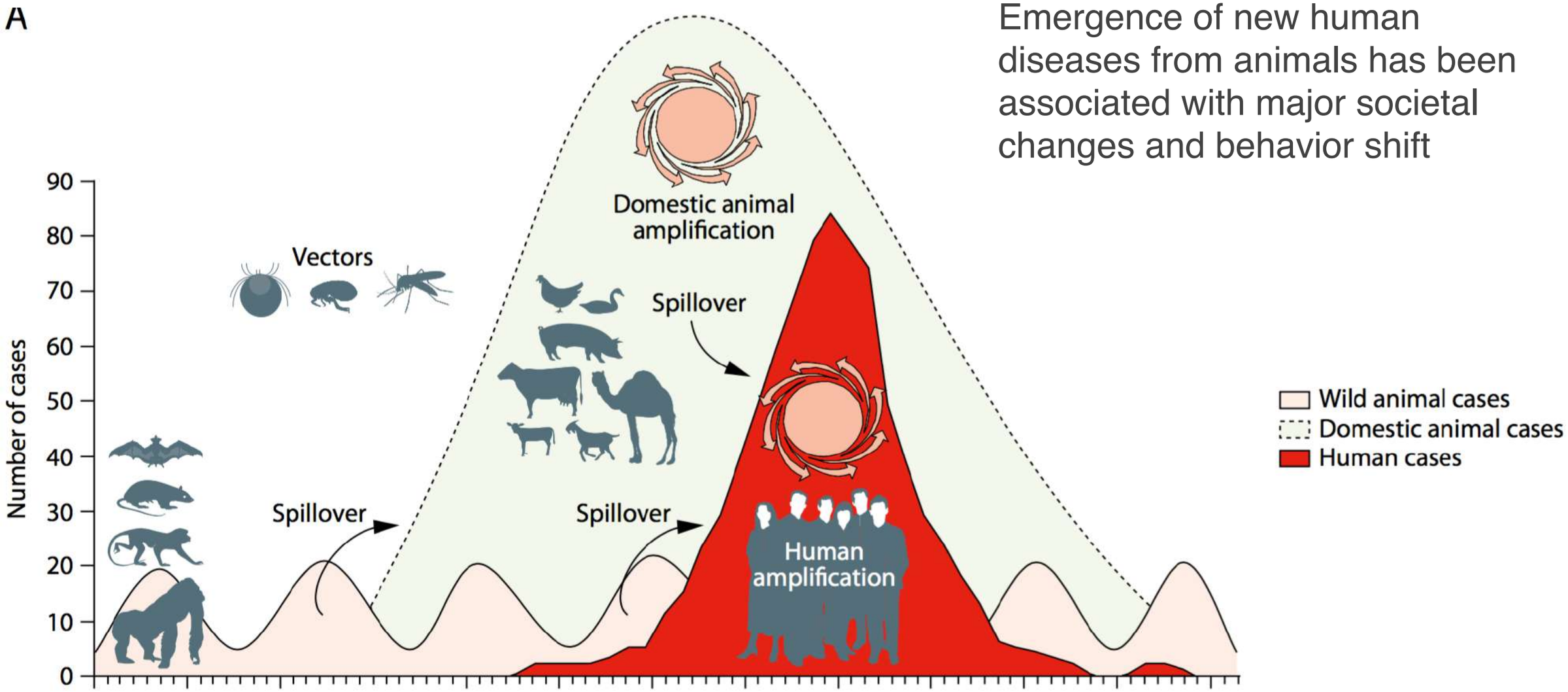
Disease landscape within interaction among host, agent and environment

- Diseases, including emerging diseases, **result** from **interactions** between infectious agents, hosts, and the environment
- Several factors lead to the development of bacterial infection and disease



Morens & Fauci, 2020

Zoonoses dynamic



Emergence of new human diseases from animals has been associated with major societal changes and behavior shift

Transmission of infection and amplification in people (bright red) occurs after a pathogen from wild animals (pink) moves into livestock to cause an outbreak (light green) that amplifies the capacity for pathogen transmission to people

United Nations Environment Programme and International Livestock Research Institute (2020)

Definition of emerging infectious diseases

Table 2. Major Categories of Emerging Infectious Diseases

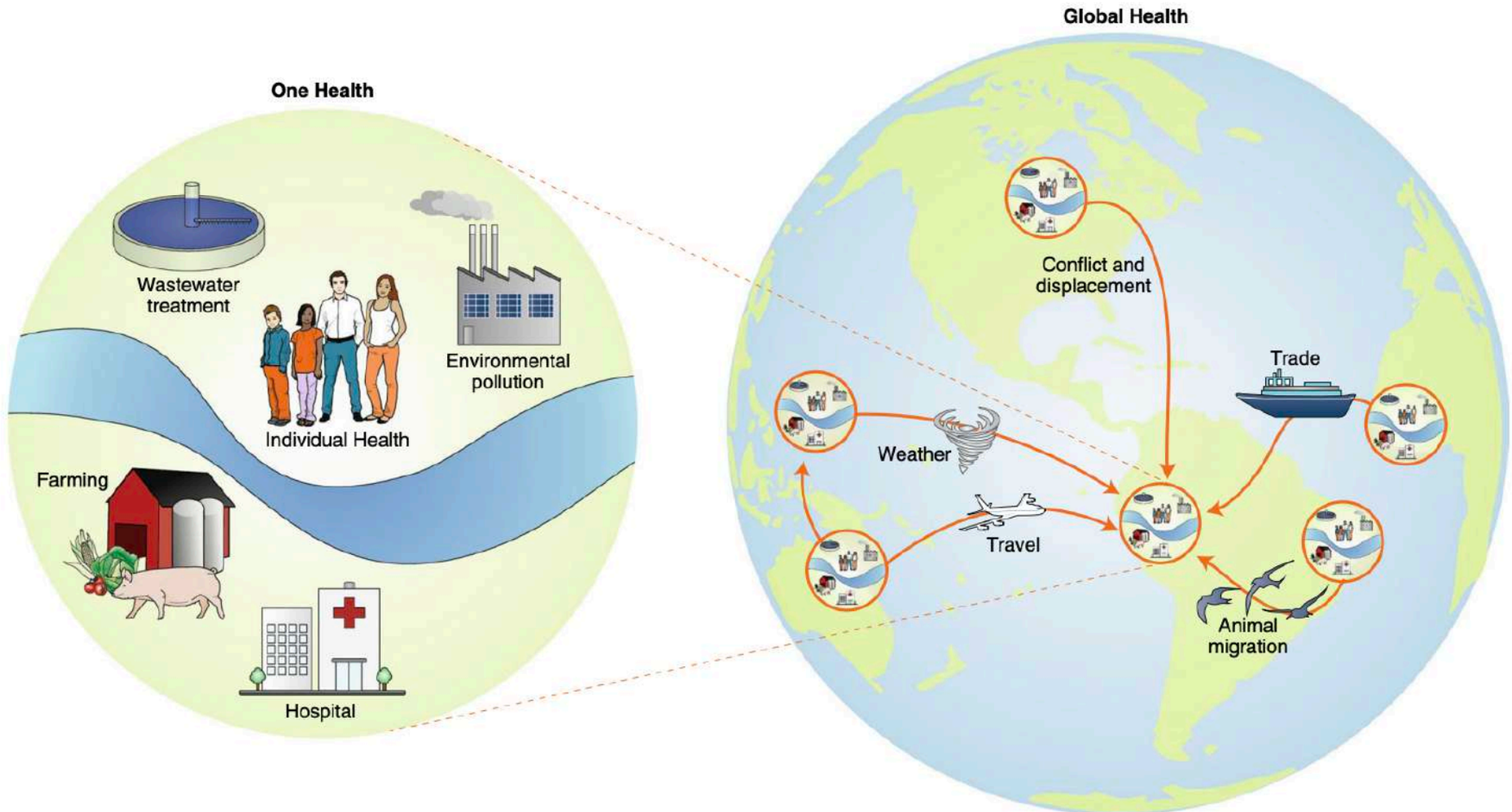
Newly emerging infectious diseases	Diseases recognized in humans for the first time, e.g., HIV/AIDS (1981), Nipah virus (1999), SARS (2002), MERS (2012), COVID-19 (2019)
Re-emerging infectious diseases	Diseases that have historically infected humans but continue to re-appear either in new locations (e.g., West Nile in the United States and Russia in 1999) or in resistant forms (e.g., methicillin-resistant *Staphylococcus aureus*)
Deliberately emerging infectious diseases	Diseases associated with intent to harm, including mass bioterrorism
Accidentally emerging infectious diseases	Diseases created by humans that are released unintentionally, e.g., epizootic vaccinia and transmissible vaccine-derived polioviruses

Not included are currently established endemic diseases that are presumed to have been newly emerging at some time in the past and then went on to develop long-term persistence in human or animal populations (see text).

One Health

Morens & Fauci, 2020

One Health and Global Health perspectives for AMR



Hernando-Amado1 et al., 2019

AMR transmission occurs at the local level across the borders between different ecosystems, such as farms, hospitals, wastewater treatment plants and natural environments

This is a One Health problem, where the health of any of these ecosystems may affect the health of the others, including human health

One Health is a ‘local version’ of Global Health, which addresses communication among local ecosystems and the global conditions that facilitate the worldwide spread of AMR

This may occur through the global interchange of goods by human travellers, migrating animals and even through the help of natural phenomena such as El Niño, which can expand the area for interchange among geographical areas

Corridors and bridges therefore exist that promote the globalization of gene spread, encouraging the appearance of similar microbial communities wherever the same processes occur