Immunity to infection (contd)

Late Immune responses

(4 days onwards)

Three type of cells are important:

1. **T cells**

2. **B cells**

3. **Macrophages**

Activation of T helper cells

- After nearly 4 days, the **specific** immune response starts.

- During the early phase **APC** have carried peptides resulting from the **degradation** of the proteins from the infecting microorganism to the **local lymph node** and presented them in **MHC bound form** to **T cells**.

- This process allows the **rare (~1 per 10^6) antigen specific T cells** to encounter the presented peptide-MHC complex as the T cells **traffic** through the lymph node.

- This is facilitated by a process termed **'shut down'.**

- It is **inhibition of exit of lymphocytes** from the local lymph node resulting in **accumulation** of cells.

Activation of B cells

- **Antigen-specific B cells** acquire antigen from APC via their **surface IgM.**

- These APCs **process and present** this antigen via their **MHC class II molecules**.

- After this presentation of antigen by APC, B cells **get activated** and **start antibody production**.

- The elements of innate response, esp. complement also plays a **significant** role in efficient antibody production.

- It has been shown that activation of the antibody response is **many times more efficient** if the antigen is **bound to C3d.**

Interactions between activated cells

- The activation of T cells leads to the **clonal proliferation** of **antigen-specific cells** such as **TH cells** and to the production of other **effector T cells**, such as **cytotoxic T cells (CTL).**

- The interaction of **specific TH cells with B cells** leads to the generation of a **primary IgM-led antibody response.**

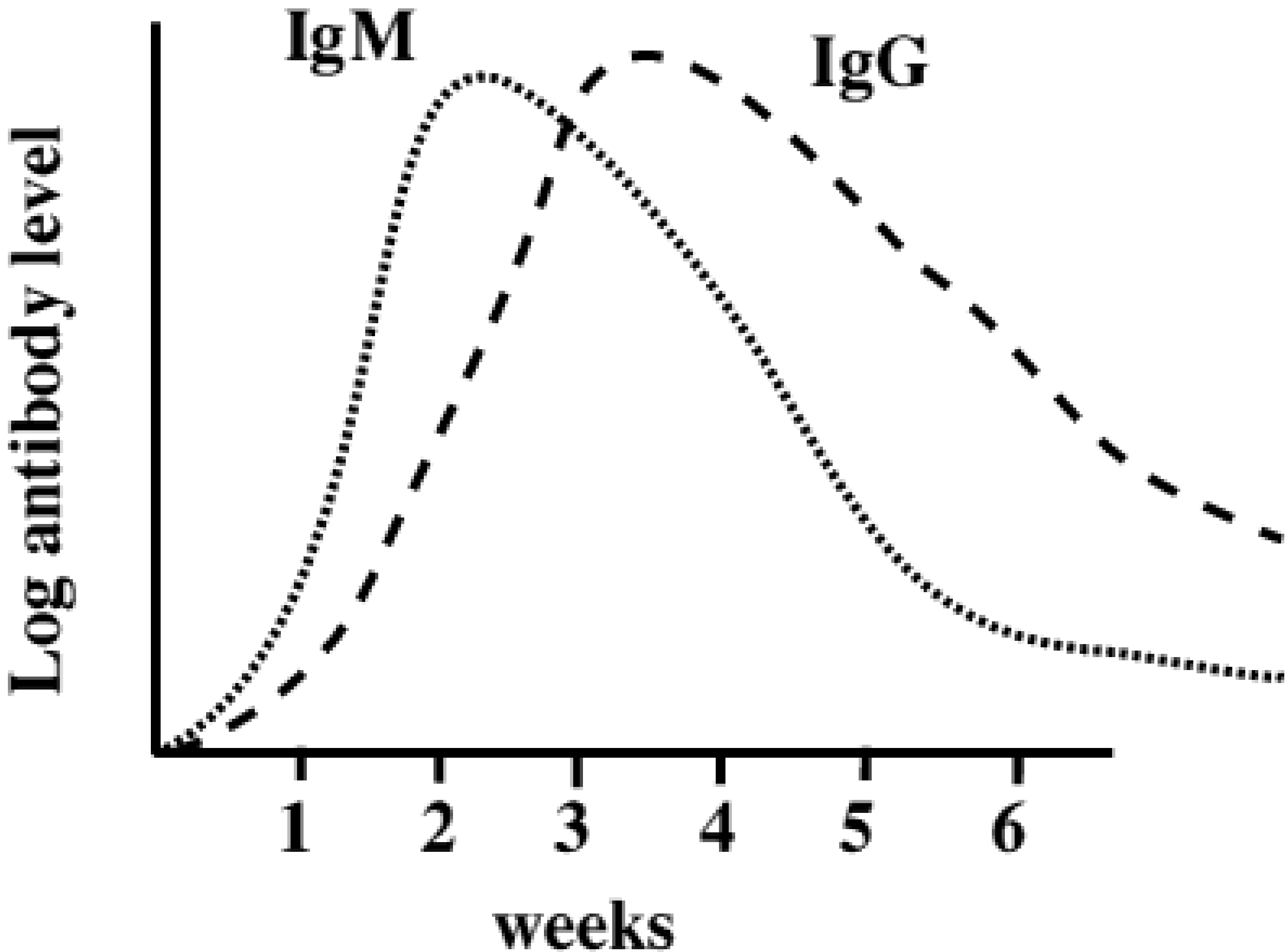
- It is **followed** by a **shift** to **higher affinity** antibodies **IgG, IgA and/or IgE production (affinity maturation).**

Specific Antibody

- **Specific antibody** clearly plays an important role in **clearing** many primary infections by making **antigen-antibody complexes** which are then **removed by immune cells**.

- The presence of **IgM** is detectable after **5 days** following antigen entry and peaks between **2-3 weeks**.

- The **IgG** response is delayed by about **4-5 days** (total 9-10 days) and persists **much longer**.


IgM
IgG
Log antibody level
1
2
3
4
5
6
weeks

- **IgM** primarily acts as an **activator of the complement system.**

- **IgG** can also activate complement but **in addition** it **signals further effector mechanisms** by attaching to the **Fc receptors** on phagocytes, eosinophils and mast cells.

Effector T cells

Essentially **two** types of **effector T cells** are vital in the clearance of different sorts of infection:

- **TH1** cells **recruit and activate macrophages** by secreting appropriate **cytokines**.
- **CTL (cytotoxic T lymphocytes)** are able to **recognize cells harbouring intracellular pathogens** which are out of reach of humoral immunity.

Summary of the phases of the immune response

	Immediate	Early	Late
	0-4hrs	4-96hrs	>96hrs
Type	Innate	Innate	Specific
Key molecules	Complement Histamine etc	Complement IL-1,TNF α,IL12 IFN α/β MBP, CRP	IgM and IgG antibody IL2,IL4,IL12,IFNγ
Key cells	Macrophages Mast cells Neutrophils	Macrophages Neutrophils NK cells	T cells B cells Macrophages

Different immune mechanisms protect against different pathogens

- The immune system has to cope with a spectrum of pathogens which have distinct lifestyles and obviously **different arms** of the immune system are needed in **different situations**.

- On top of this, many pathogens have **evolved specific counter measures** which **limit or inhibit** the effectiveness of the immune response.

We can divide the types of pathogens as follows:

Extracellular organisms

- **bacteria**
- **multicellular eukaryotes (parasites)**

Intracellular organisms

- **bacteria**
- **protozoa**
- **viruses**

Extracellular organisms

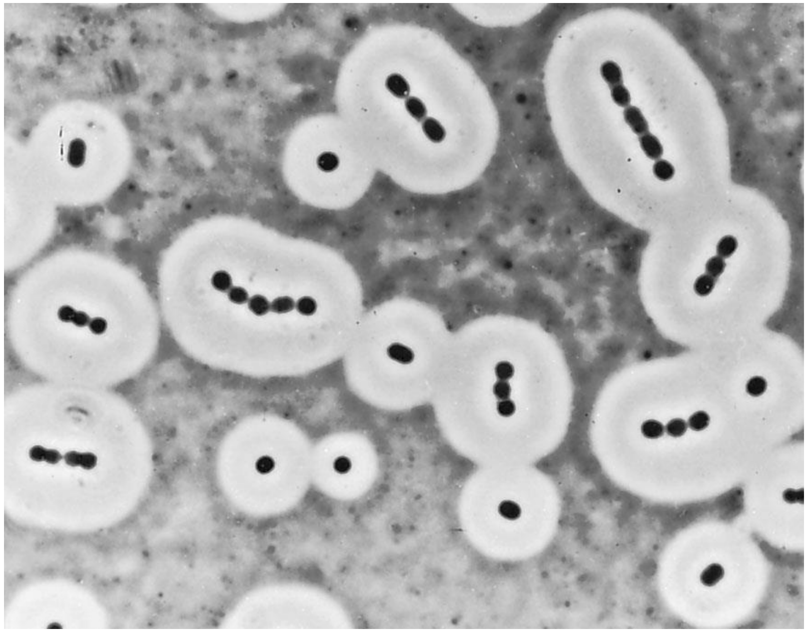
Bacteria

- These are the **simplest type of organism to combat** and in many cases the innate immune system may be able to clear an infection using complement and phagocytosis only.

- **Specific antibody** is highly effective, both by directing **complement lysis** and inducing **opsonisation and phagocytosis.**

- Some bacteria have evolved **capsules** which prevent recognition by innate mechanisms.

- They require **both antibody and complement opsonisation** to promote efficient clearance by phagocytes.



- Where **toxins** are produced, **antibody** is of course vital to **neutralize** them **(antitoxins),** e.g., tetanus antitoxin in critical tetanus patients.

- **IgA** plays an important role against organisms that infect **mucosal surfaces** (respiratory tract, gut, genito-urinary tract).

Parasites

- **Large, multicellular parasites** present a special problem to the immune system and indeed are rather **poorly eliminated**.

- The mechanisms deployed include **antibody directed complement attack** and **ADCC (**antibody-dependent cellular cytotoxicity), in particular by **eosinophils**.

- Innate immunity is generally **ineffective**.

- The parasites employ many **evasion strategies** including complement inhibitors, release of large quantities of **soluble antigen** (which is difficult for antibodies to interact with) and **acquisition of host proteins** (to deceive immune system).

Intracellular organisms

Bacteria and Protozoa

- Many bacteria have **evolved resistance** to the killing mechanisms used by phagocytes.

- These pathogens actively replicate inside bacteria, either in the **phagosome** or, in some cases in the cytoplasm where a specific adaptive mechanism has been acquired,.

- This type of bacteria **cannot be eliminated** by **immediate** immune mechanisms.

- **T cell activation** is required and a **TH1 response** is necessary for clearance of the organism.

- **Memory T cells** are the **key players** in protecting against most intracellular bacteria and parasites.

Viruses

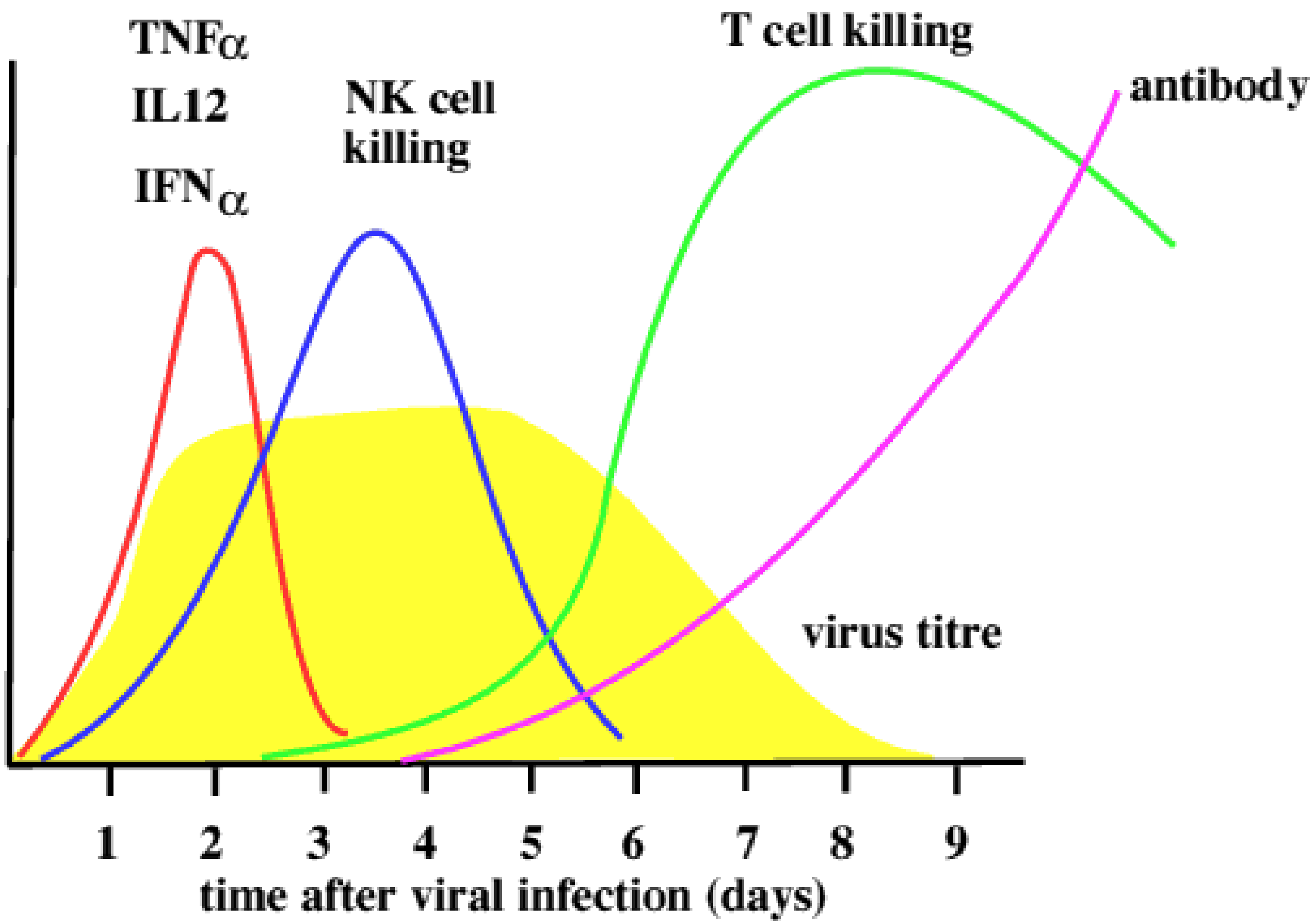
- Viruses are a very diverse group of **obligate intracellular pathogens.**
- Almost **every form of immunity** comes into play against some types of virus.
- **Enveloped viruses** can be damaged by **complement attack**, and some directly bind **C1q** or **homologous collectins.**
- **Phagocytes** can take up and **destroy antibody and complement coated viruses.**

Collectins are **soluble** pattern recognition receptors (PRRs).

The **key players** in antiviral immunity are:

- **Interferon**
- **NK cells**
- **Antibody**
- **TH1 cells**
- **CTL (cytotoxic T lymphocytes)**

Cytokines and NK cells combine to provide early defense against virus infections



- Protection against **subsequent challenge** varies with the behaviour of the virus but **specific antibody is highly effective** in preventing reinfection.

" If you feel pain, you're alive. If you feel other people's pain, you're a human being "

–Leo Tolstoy

Did the Great Wall of China protect the Chinese from invaders?


Thank You!