Antimicrobials and Immunization

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Antibiotic/Antimicrobial

- Antibiotics: Chemicals produced by a microorganism that kill or inhibit the growth of another microorganism
- Antimicrobial agents: Chemicals that kill or inhibit the growth of microorganisms

Brief history

- **The term "antibiotics" originally was used to denote formulations derived from living organisms but is now used for partially or wholly synthetic antimicrobials too.**

- **The first antibiotic (in the original sense of the word) was penicillin.**

- **Alexander Fleming was the one who discovered that *Penicillium* kills bacteria in 1928.**

- **Florey and Chain resurrected Fleming's work in the 40s, isolated penicillin, and by WWII were treating millions with antibiotics.**

Ernst Chain

Howard Florey

Classes of antimicrobials

- Antimicrobials are classified according to the type of organism they act on:

1. Antibacterial
2. Antiviral
3. Antifungal
4. Antiprotozoal
5. Antihelmintic

Antimicrobial spectrum of activity

TABLE 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs

Prokaryotes				Eukaryotes			
Mycobacteria*	Gram-Negative Bacteria	Gram-Positive Bacteria	Chlamydias, Rickettsias†	Fungi	Protozoa	Helminths	Viruses
		←Penicillin→		←Ketocon-azole→		←Niclosamide→ (tapeworms)	
←Streptomycin→					←Mefloquine→ (malaria)		
							←Acyclovir→
						←Praziquantel→ (flukes)	
	←Tetracycline→						
←Isoniazid→							

*Growth of these bacteria frequently occurs within macrophages or tissue structures.
†Obligately intracellular bacteria.

J. Decker, University of Arizona

- No antimicrobial is effective against all microbes

Examples of important antiviral agents

- **Rimantadine/ Amantadine:** Targeting uncoating of influenza A virus by inhibiting viral M2 protein
- **Tamiflu (oseltamivir), Relenza (Zanamivir):** Neuraminidase inhibitors targeting influenza virus (A & B) surface protein for cell-to-cell traffic
- **Acyclovir, famciclovir:** Herpes simplex, Varicella zoster
- **Ribavirin:** Influenza A & B, RSV, Togavirus (e.g.Rubella)
- **Zidovudine (AZT), Didanosine(ddi), Lamivudine:** Nucleoside RT inhibitors (NRTI) for retroviruses (HIV)
- **Nevirapine (Viramune):** Non-nucleoside RT inhibitors (NNRTI) for HIV
- **Ritonavir, Kaletra:** protease inhibitors (PI) for blocking the function of the HIV protease
- Remdesivir (nucleoside analogue) and ritonavir-boosted nirmatrelvir (Paxlovid, proteases inhibitors) for the treatment of COVID-19

Mode of action of antibacterial agents

- Bacteria have their own enzymes for
  - Cell wall formation
  - Protein synthesis
  - DNA replication
  - RNA synthesis
  - Synthesis of essential metabolites

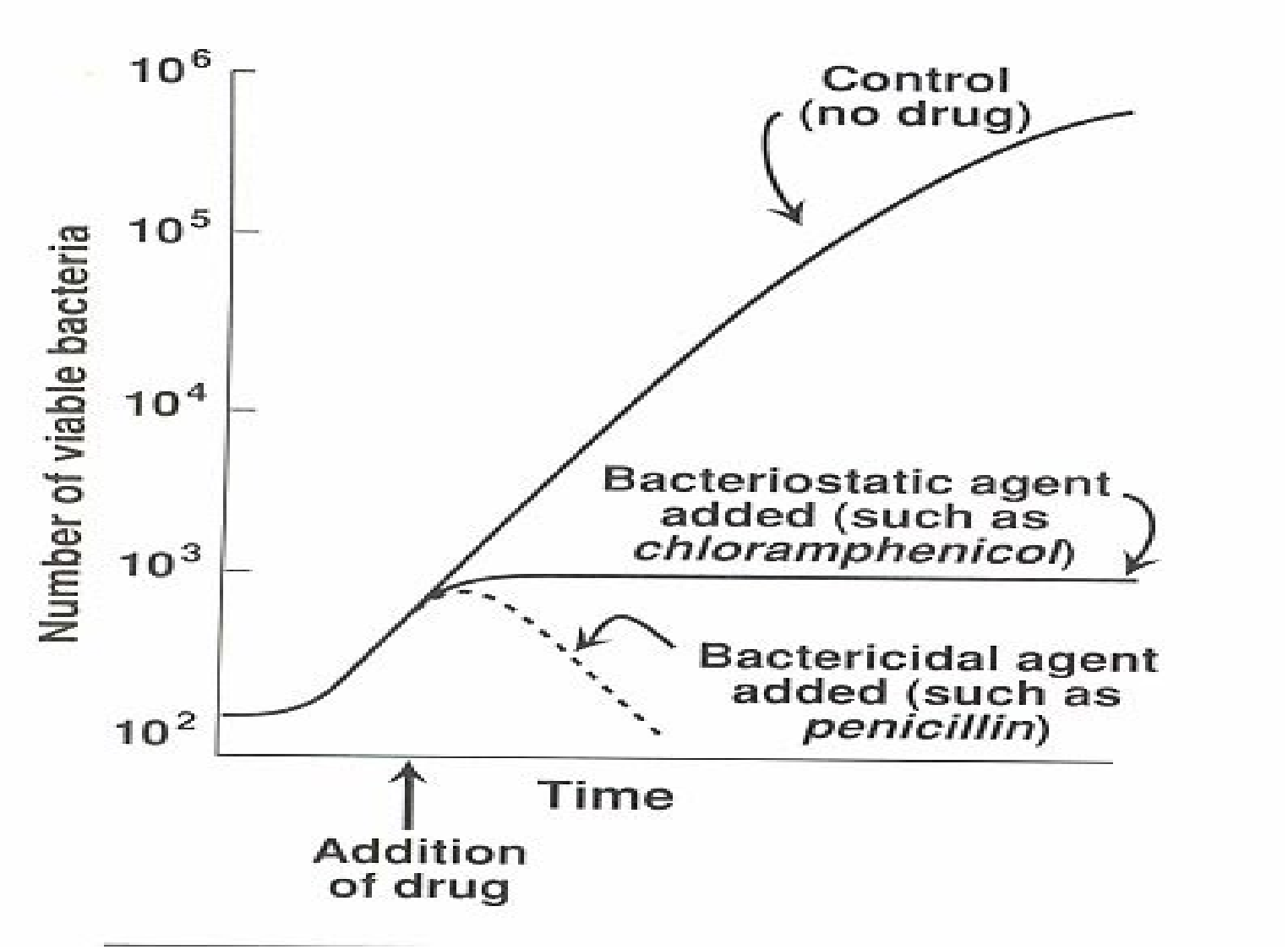
MIC

- Minimum Inhibitory Concentration
- Smallest concentration (μg/ml) of drug that stops bacterial growth (bacteriostatic)
- Reversible
- Sensitivity ***in vitro***

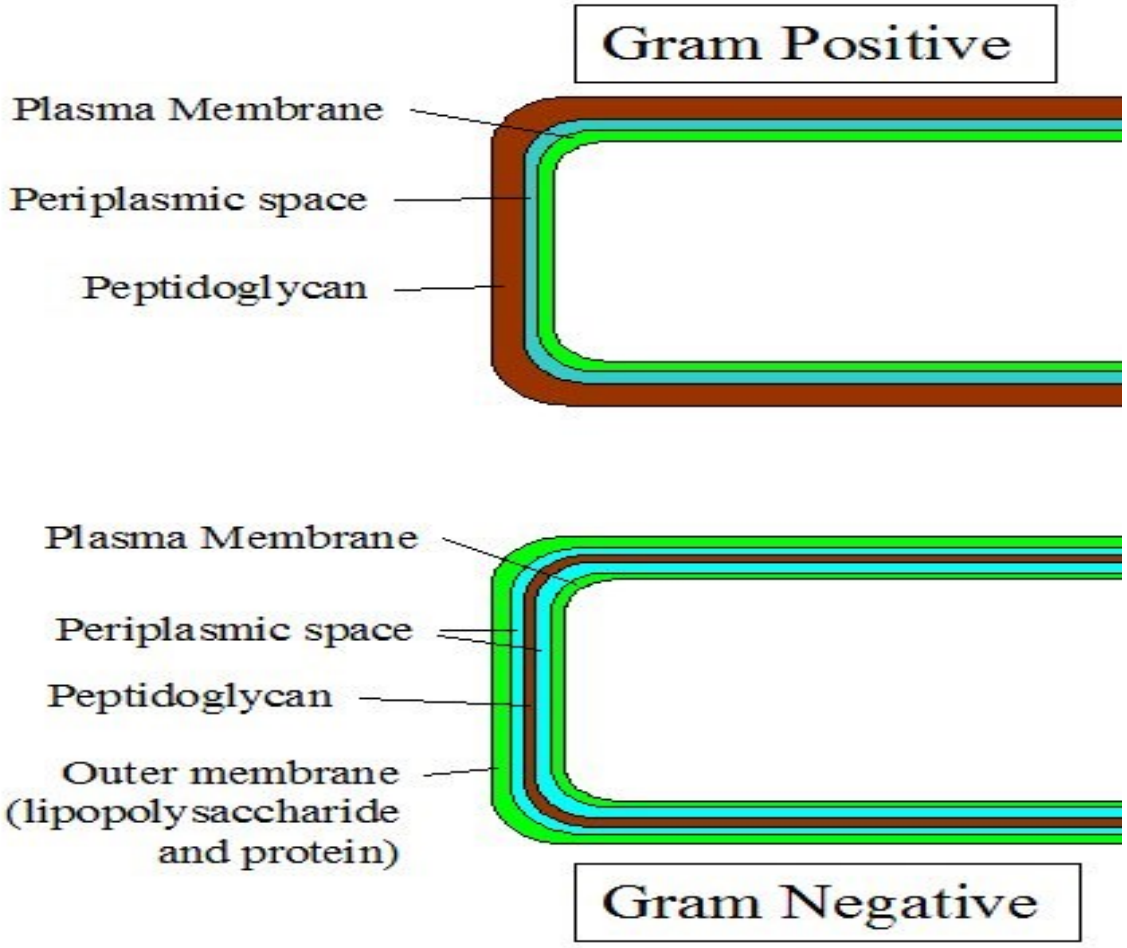
MBC

- Minimal Bactericidal Concentration
- Smallest concentration that irreversibly kills microbes
- No re-grow even if the drug is removed

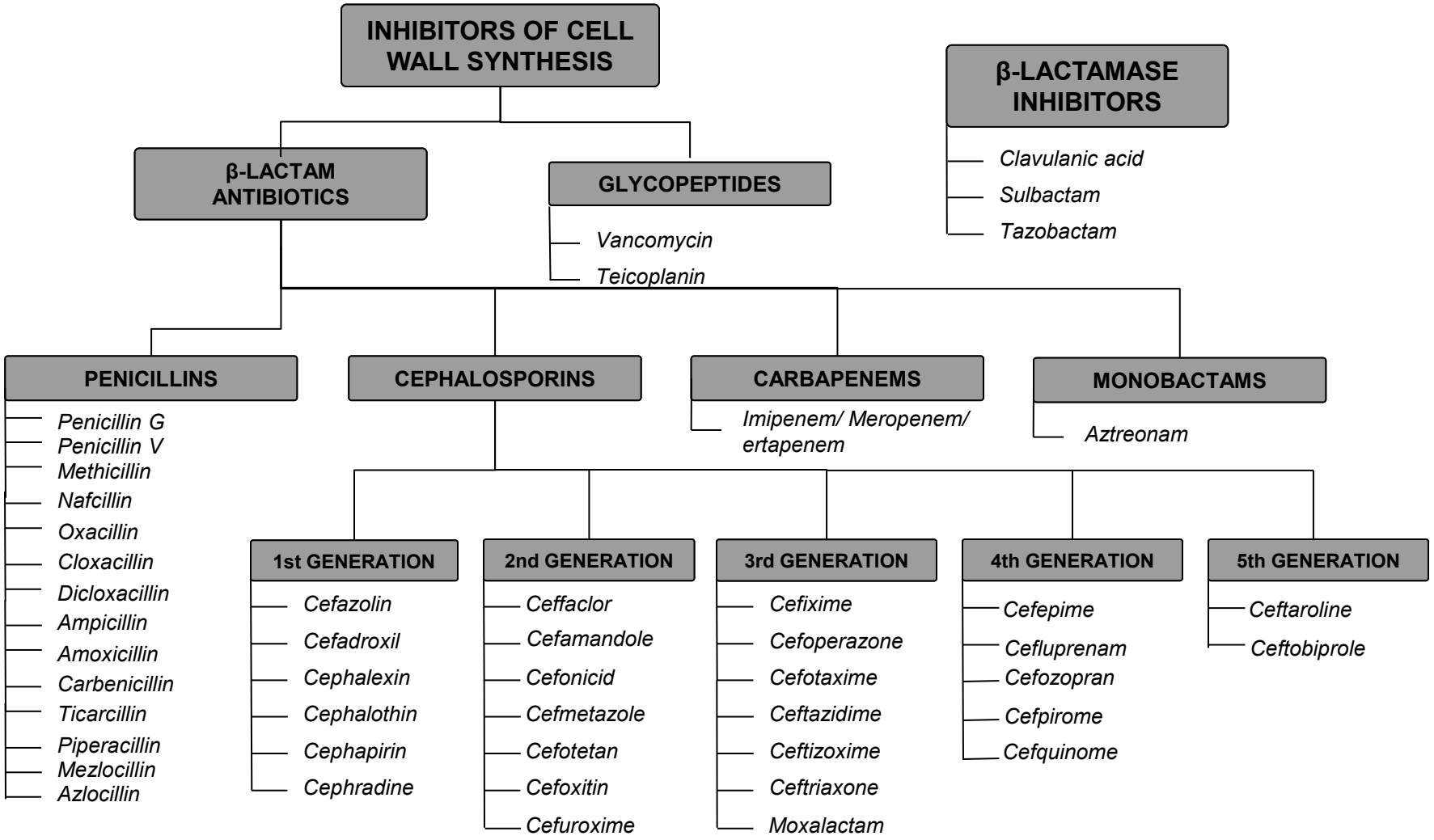
Bacteriostatic and Bactericidal



Prokaryotic cell walls



Inhibitors of cell wall synthesis

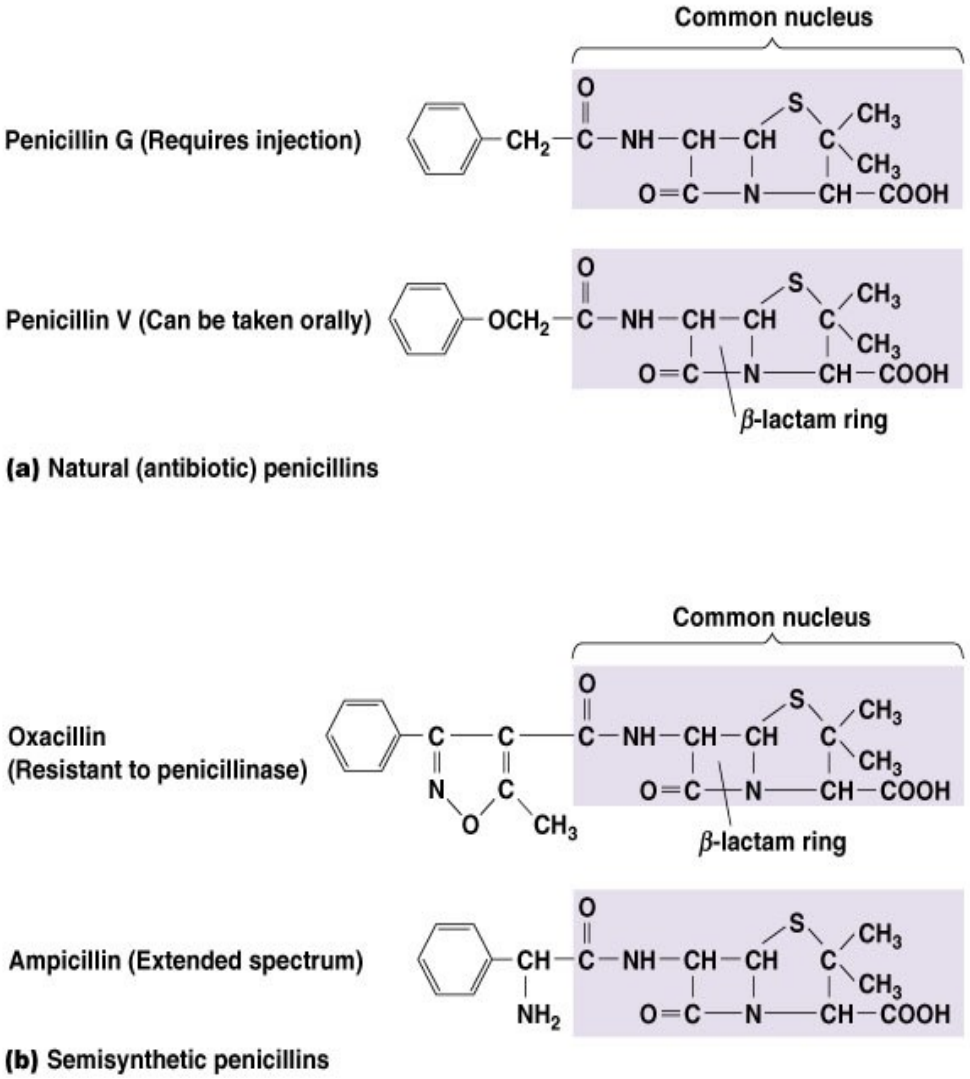


Penicillins

- Derived from the fungus *Penicillium spp.*
- Interfere with peptidoglycan cross-linking
- Selective to bacteria only (cell wall)
- No effect on mammalian cells
- 2% allergy, 0.002% Fatal
- Intravenous/ intramuscular (unstable in gastric acid)
- Therapeutic concentration in most tissues
- Poor cerebrospinal fluid (CSF) penetration

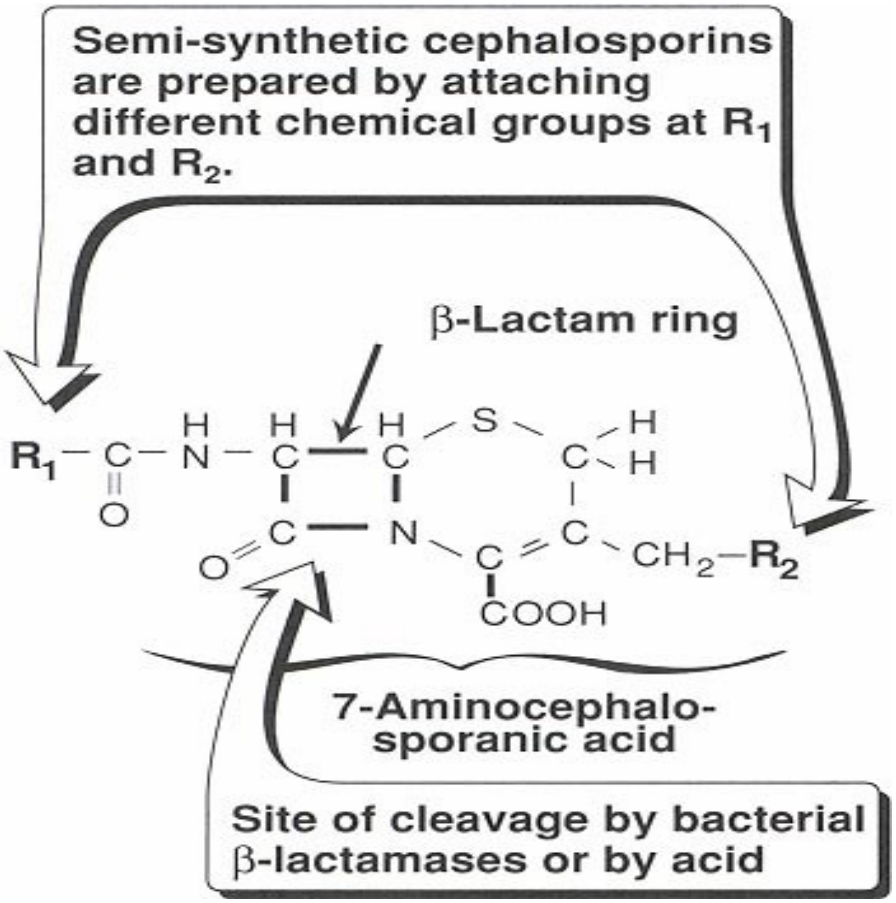
Penicillins

- Penicillin and related antibiotics (over 50 compounds)
  - Share 4-sided ring (β-lactam ring)
- Natural penicillins
  - Narrow range of action
  - Susceptible to penicillinase (β-lactamase)



Cephalosporins

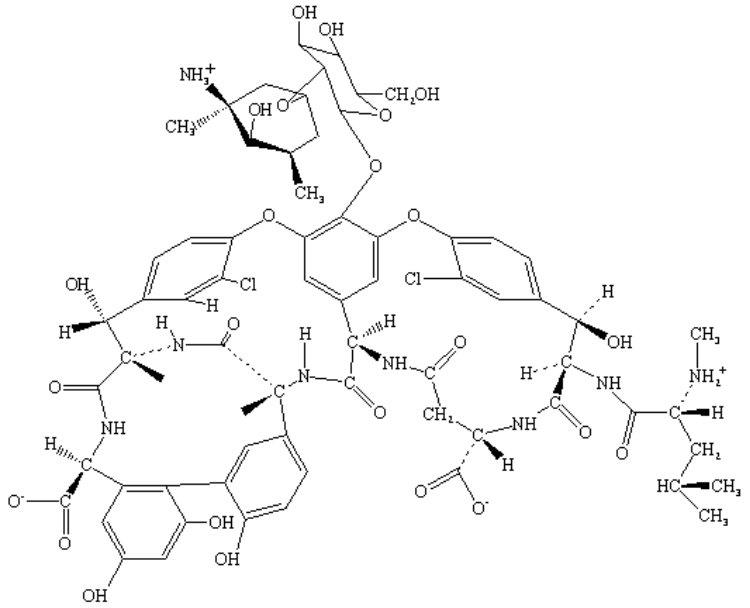
- Structurally similar to penicillins
- Isolated from *Cephalosporium acremonium*
- Therapeutic concentration in many tissues, 3rd and 4th generation cephalosporins can penetrate CSF



Cephalosporins

- **First generation: e.g. Cephalexin, Cephradine**
- Better on Gram positive organisms: e.g. *Staphylococcus, Streptococcus*
- Gram negative organisms: e.g. *E.coli, Klebsiella*
- **Second generation: e.g. Cefuroxime, Cefoxitin**
- More Gram-negative organisms & anaerobes: e.g. *Haemophilus, Gonococcus*
- **Third generation: e.g. Cefotaxime, Ceftazidine, Cefixime, Ceftibuten**
- Better on Gram negative rods: e.g. *Pseudomonas, Providencia* and oral anaerobes
- **4th generation also available with added antimicrobial spectrum**
- **5th generation: added anti-MRSA activity.**

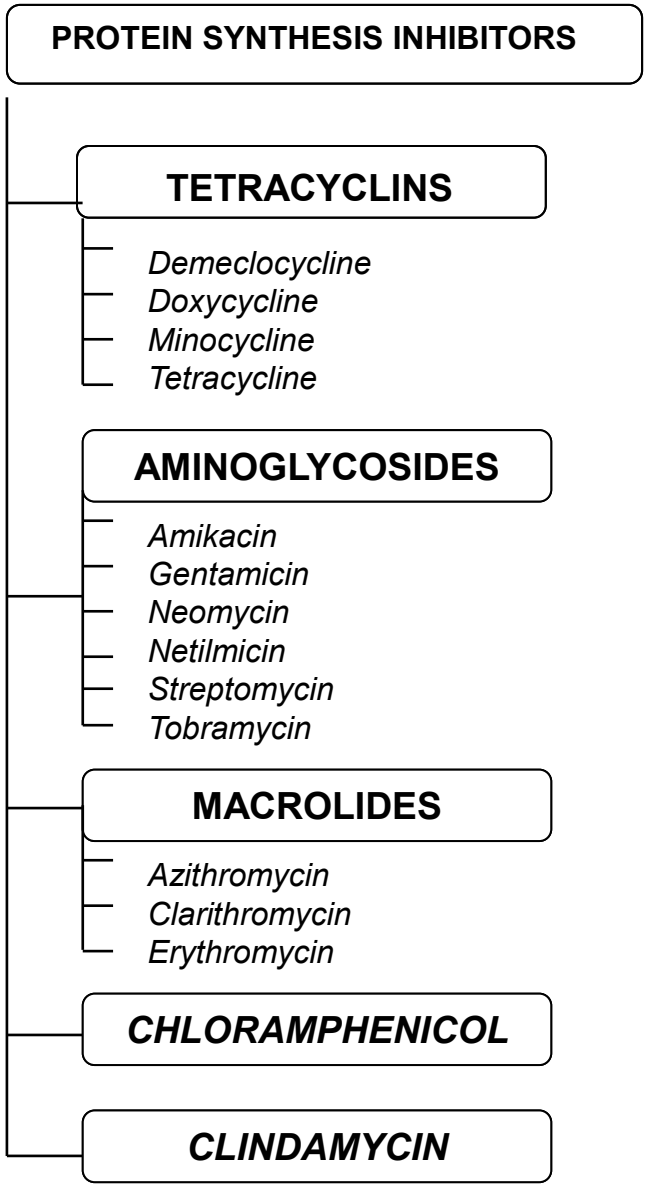
Glycopeptides: Vancomycin/Teicoplanin



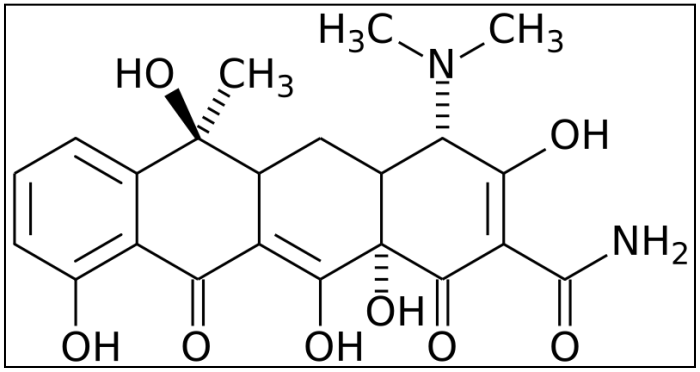
- Tricyclic glycopeptide
- Inhibits synthesis of phospholipids and cross-linking of peptidoglycans
- Activity against Gram-positive organisms
- Useful for β-lactam resistant infections
- Widely distributed, penetrates CSF

Protein Synthesis Inhibitors

- Human Ribosome
  - 80S
    - 40S
    - 60S
- Bacterial Ribosome
  - 70S
    - 30S
    - 50S



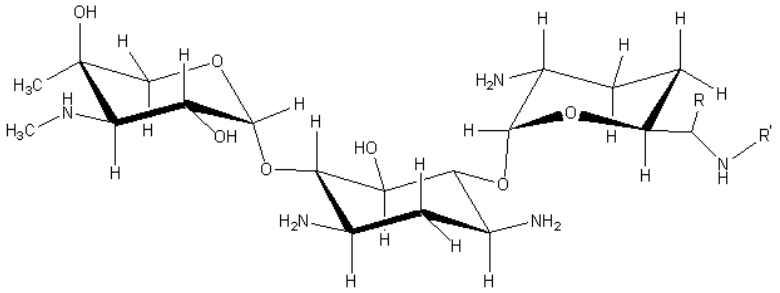
Tetracyclines



- Isolated from *Streptomyces*
- Reversibly bind 30S ribosomal subunit
- Penetrate sinus mucosa, saliva and tears

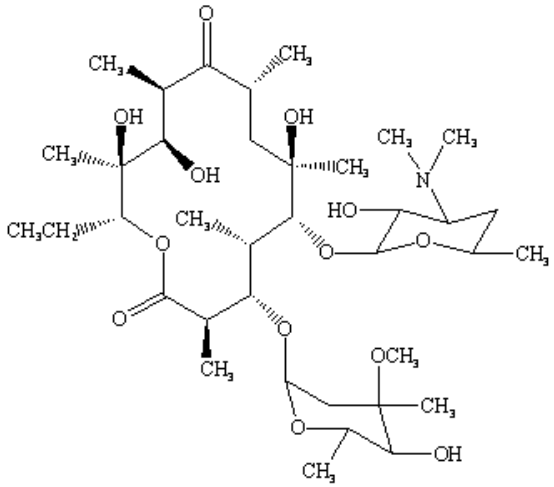
Aminoglycosides:

Gentamicin, Streptomycin, Tobramycin, Amikacin



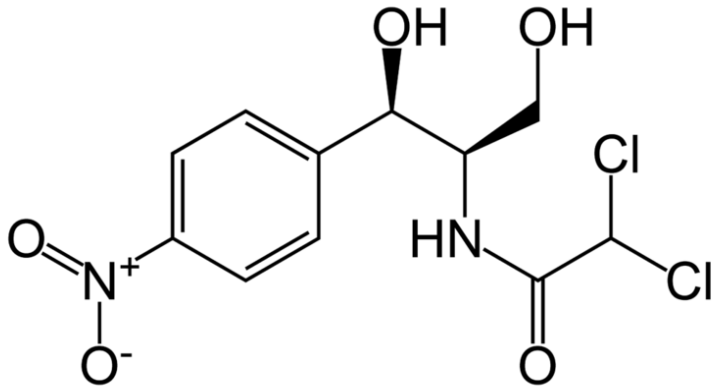
- Bactericidal for Gram-negative organisms
- Derived from *Streptomyces* and *Micromonospora*
- Irreversible binding to 30S subunit
- Actively transported into bacterial cells
- Poor gut absorption

Macrolides: Erythromycin, Clarithromycin, Azithromycin



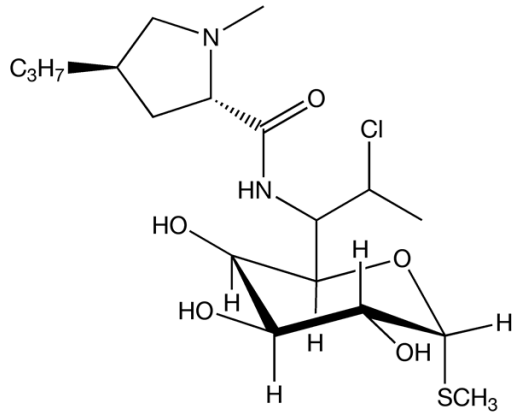
- Macrocyclic lactone structure
- Reversible binding to 50S subunit
- Therapeutic concentrations in oropharyngeal and respiratory secretions
- No CSF penetration

Chloramphenicol



- Isolated from *Streptomyces*
- Reversible binding to 50S subunit
- Broad spectrum of activity
- Indicated for severe anaerobic infections or unresponsive life-threatening infections
- Widely distributed, enters CSF

Clindamycin



- Semisynthetic derivative of Lincomycin
- Reversible binding to 50S subunit
- Covers anaerobes and Gram positive aerobes
- Widely useful for head and neck infections
- Penetrates saliva, sputum, and bone, but not CSF

Inhibitors of Nucleic Acid Function/Synthesis

- Fluoroquinolones
  - Bind bacteria DNA gyrase (topoisomerase II)
  - Concentrate in sinus and middle ear mucosa, penetrate cartilage and bone

- Rifamycins
  - Bind to DNA-dependent RNA polymerase and block the synthesis of mRNA.
  - Cross the blood–brain barrier and reach high concentrations in saliva

Inhibitors of Metabolism

- Sulfonamides
- Trimethoprim
- Interfere with the production of folic acid coenzymes that are required for purine and pyrimidine synthesis

Antimicrobial resistance

- **Methicillin resistant *Staphylococcus aureus (MRSA)***: simultaneously resistant to many antibiotics including most β-lactams (except anti-MRSA cephalosporins). Some sensitive only to vancomycin, in which case only some newer drugs may be used (Linezolid**).**
- **Extended-spectrum β-lactamases *(ESBL)***: inactivate most β-lactams (except carbapenems) . Found in *Klebsiella pneumoniae, E. coli, Enterobacter, Salmonella,* etc.
- **Penicillin resistant *S. pneumoniae (PRSP)***
- **Multi-resistant *S. pneumoniae (MRSP)***
- **Vancomycin intermediate resistant *S. aureus* (*VISA)***
- **Vancomycin resistant *S. aureus (VRSA)***

Wide-spread and indiscriminate use of antibiotics!!

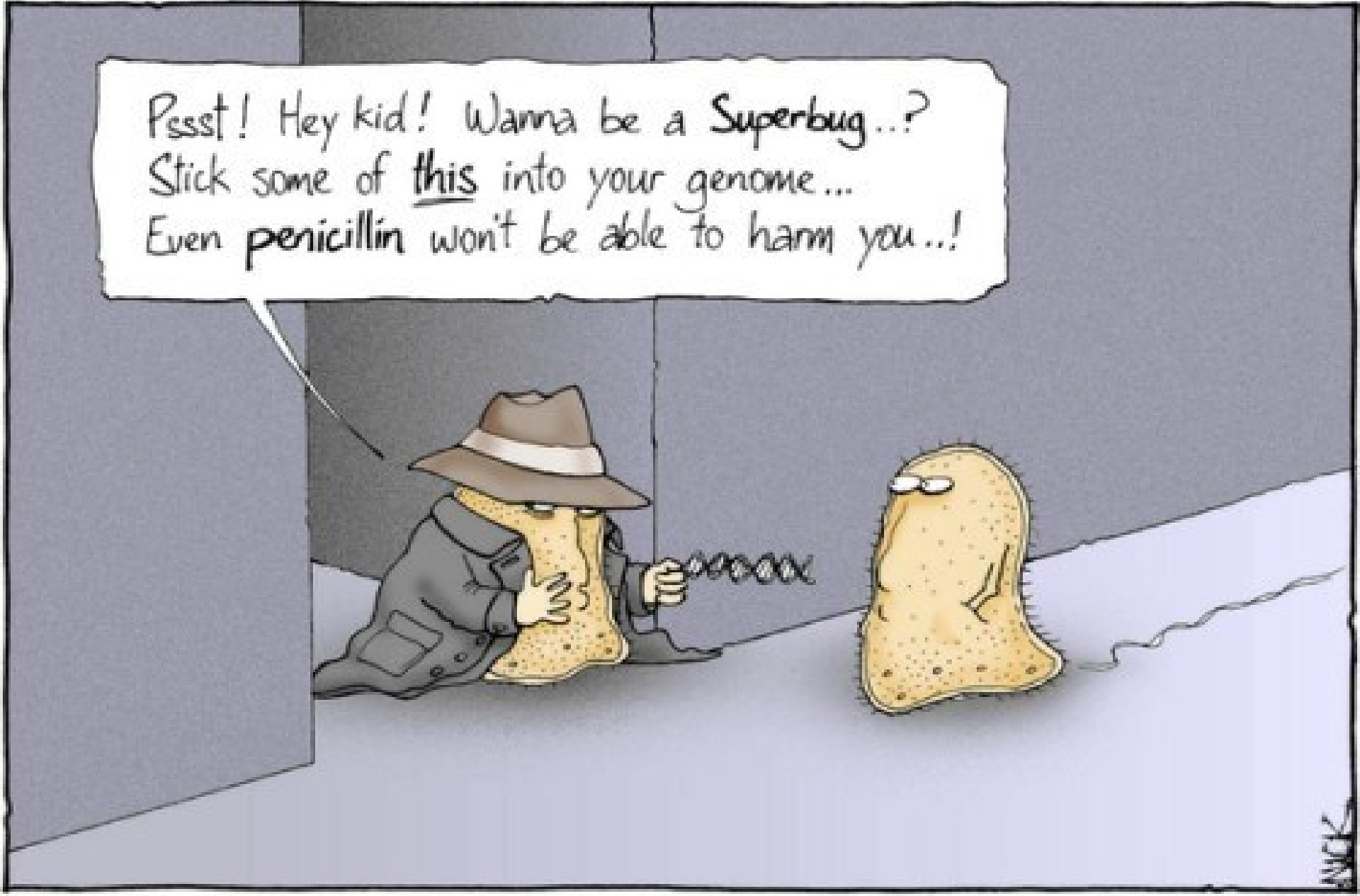
Antimicrobial resistance

1.Intrinsically resistant

- Impermeable to the drug
- Lack of target binding site
- Production of enzymes that can destroy antibiotics

2.Acquired resistance (genetic modification)

- Mutations that alter permeability to the antibiotic
- Mutations that alter the target site
- Switch on a gene of an enzyme that can destroy the antibiotic
- Acquiring a gene (e.g., on a plasmid), the product of which can destroy the antibiotic



It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

Immunization

Immunization is the process by which an individual's immune system is fortified by natural (e.g. infection) or artificial (e.g. vaccination) means against foreign agents.

- Vaccination is very cost-effective as a public health measure, saving many lives (immunization saves an estimated 2.5 million deaths each year from diphtheria, tetanus, pertussis and measles).
- Many others die from infectious diseases such as HIV for which there is as yet no effective vaccine, so new vaccines are also needed

The Concept of Vaccination

- The English physician Edward Jenner (1749-1823) is regarded as the founder of modern vaccination, but he was by no means the first to try the technique.
- The ancient practice of 'variolation' dates back to tenth-century China and arrived in Europe in the early eighteenth century via Turkey.
- The technique involved the inoculation of children with dried material from healed scabs of mild smallpox cases and was a striking foretaste of the principles of modern attenuated viral vaccines.
- Jenner's innovation was to show that a much safer and more reliable protection could be obtained by deliberate inoculation with cowpox (vaccinia) virus.
- Milkmaids exposed to cowpox were traditionally known to be resistant to smallpox and so retained their smooth complexions.

The principle and Aim of Vaccination

- The principle of vaccination is simple: to prime the adaptive immune system to the antigens of a particular microbe so that on first contact with the live organism a rapid and effective secondary immune response will be induced by memory T and B cells.
- Vaccination therefore depends upon the ability of lymphocytes, both B and T cells, to respond to specific antigens and develop into memory T and B cells and represents a form of actively enhanced adaptive immunity.
- The most ambitious aim of vaccination is eradication of the disease.
- This has been achieved for smallpox, the eradication of polio is being attempted.
- However, as long as any focus of infection remains in the community, the main effect of vaccination will be protection of the vaccinated individual against infection.

The importance of herd immunity

- Successful vaccination programs rely not only on the development and use of vaccines themselves, but also on an understanding of the epidemiologic aspects of disease transmission.
- If enough individuals in a population are immunized, this will reduce or stop transmission of the infection.
- This is called **herd immunity**. By having your own child immunized, you therefore help protect the whole community – but conversely, when too many parents decide that their child will not be immunized, because they think the risk of their child getting the disease is low, this may contribute to the disease becoming more common.
- It is therefore important to know how many individuals in a population must be immunized to produce herd immunity, and also whether immunity should be boosted by re-vaccination.

Types of vaccine	Examples
Live attenuated	
Viral	Measles, mumps, rubella, vaccinia, varicella, yellow fever, zoster, oral polio, intranasal influenza, rotavirus
Bacterial	BCG, oral typhoid
Inactivated	
Whole virus	Polio, influenza, hepatitis A, rabies
Whole bacteria	Pertussis, cholera, typhoid
Fractions	
Toxoids	Diphtheria, tetanus
Protein subunits	Hepatitis B, influenza, acellular pertussis, human papillomavirus
Polysaccharides	Pneumococcal, meningococcal, *Salmonella typhi* (Vi), *Haemophilus influenzae* type b
Conjugates	*Haemophilus influenzae* type b, pneumococcal, meningococcal

Note that not all types of vaccine are available in all countries. Vaccines are also available for bioterrorism agents such as anthrax and plague, and for vaccinia.

Vaccine Safety

Both living and non-living vaccines require rigorous quality and safety control. Some common problems are listed below:

Live attenuated vaccines

- Insufficient attenuation
- Reversion to wild type
- Administration to immunodeficient patient
- Persistent infection
- Contamination by other viruses
- Fetal damage

Non-living vaccines

- Contamination by toxins or chemicals
- Allergic reactions
- Autoimmunity

Genetically engineered vaccines

- Possible inclusion of oncogenes

Passive Immunization with Antibodies

- Before the introduction of antibiotics, acute infectious diseases were often treated by the injection of preformed antibody on the principle that the patient was already ill, and it was too late for 'active' vaccination.
- The demonstration that immunity to tetanus and diphtheria could be transferred to mice with serum from vaccinated rabbits was a key experiment in the discovery of antibody in the 1890's.
- Subsequently, the production of antiserum for the passive treatment of diphtheria, tetanus and pneumococcal pneumonia, and against the toxic effects of streptococci and staphylococci, became an important industry, and generations of horses that had retired from active duty were kept on as the source of 'immune serum'.
- One type of passive immunity which occurs naturally is the passing of antibodies from a mother through placenta or breast milk to the infant.

Learning Outcomes:

Antimicrobials and immunization are important for treating/preventing human diseases. After taking the lecture, the students should be able to:

1. Appreciate the history of antimicrobials development.
2. Know different classes of antimicrobials.
3. Understand the basic structure of a bacterium and basic terminologies used in medical microbiology (MIC, MBC, Bactericidal, etc.)
4. Understand the phenomenon of antimicrobial resistance and its consequences.
5. Understand the concept of immunization.
6. Know the types of vaccines and vaccine-preventable diseases.
7. Understand the role of vaccines in reducing burden of diseases and eradication of diseases.