

Unit 7: Vaccine Delivery Systems

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7.1 Vaccines: the basics this unit builds on

A **vaccine** is a preparation of antigen (killed or live attenuated organism, a subunit or toxoid, a polysaccharide conjugate, or genetic instructions such as mRNA in a lipid carrier) given to produce active immunity before natural infection. The delivery problem is different from every other unit: the dose is meant to meet the immune system, in microgram amounts, usually once or a few times, and the response, not a plasma level, is the product.

Types in brief: live attenuated (measles, BCG, oral polio), inactivated whole organism (hepatitis A, inactivated polio), subunit and recombinant (hepatitis B surface antigen, HPV virus like particles), toxoids (tetanus, diphtheria), polysaccharide and conjugate vaccines (pneumococcal, Hib, meningococcal), viral vector vaccines, and nucleic acid vaccines (mRNA in lipid nanoparticles, the COVID 19 generation of products). Adjuvants such as aluminium salts, oil in water emulsions and newer immune stimulants are part of the delivery system in the wide sense: they shape how antigen is presented.

7.2 Uptake of antigens

For a vaccine to work, antigen must be taken up by **antigen presenting cells** (dendritic cells above all, also macrophages and B cells). The sequence to learn:

Antigen Uptake by M Cells

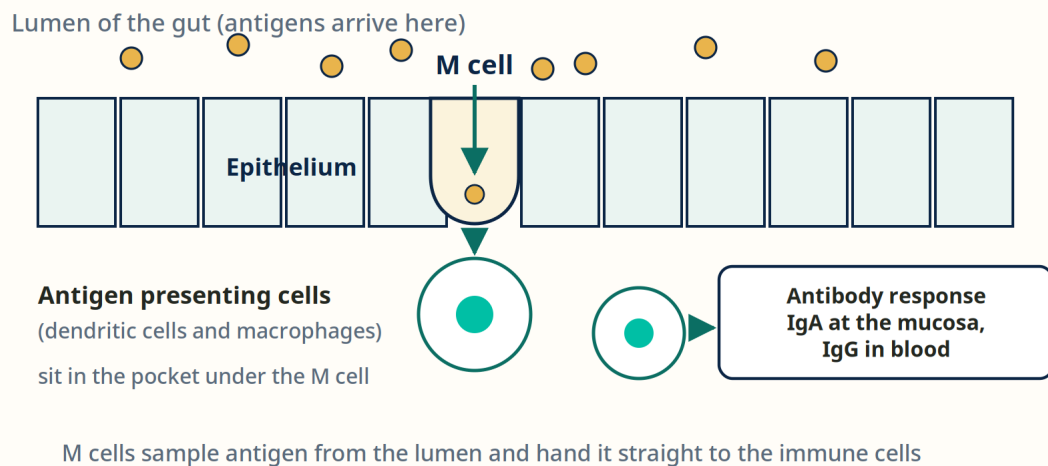


Figure: M cells sample antigen from the mucosal surface and hand it to antigen presenting cells, starting the antibody response.

Uptake of antigen and the start of the immune response
 Antigen deposited (muscle, skin or mucosa)
 -> dendritic cells capture antigen by phagocytosis, endocytosis
 or (for particulate vaccines) size dependent uptake
 -> dendritic cells mature and migrate to the draining lymph node
 -> antigen is processed and presented on MHC molecules
 (MHC class II to helper T cells, class I cross presentation to killer T cells)
 -> T cells activate, help B cells, antibodies and memory cells are produced
 Delivery levers: particle size (about 20 to 200 nm drains freely to lymph nodes,
 larger particles are carried by cells), antigen persistence at the site,
 adjuvant signals that mature the dendritic cell, and route of delivery.

Two formulation consequences follow. **Particulate antigens are taken up far better than soluble ones**, so adsorbing antigen on alum, forming virus like particles, liposomes and polymer particles is a delivery decision, not decoration. And **the route decides the flavour of immunity**: injection gives strong systemic IgG, mucosal delivery can add secretory IgA at the surface where many pathogens enter.

7.3 Single shot vaccines

A **single shot vaccine** aims to deliver, in one administration, the effect of a prime dose plus its boosters. The design logic: the first fraction of antigen is available immediately (the prime), and later fractions are locked inside biodegradable microspheres or particles engineered to break down at staggered times (weeks to months later), releasing pulse doses that act as boosters without another clinic visit.

- **Technology used:** PLGA and related biodegradable polymer microspheres of different polymer composition, molecular weight and size, each population timed to erode and release its antigen pulse at a set interval; antigen stability inside the degrading, acidifying microsphere is the central technical difficulty and is managed with stabilisers and buffering excipients.
- **Why it matters:** missed booster doses are a leading cause of incomplete immunisation in real programmes; a single visit product also reduces cold chain trips, needles and record keeping.
- **Honest status:** single shot tetanus and other candidates have been demonstrated in animals and early studies, but antigen damage during encapsulation and storage, and dose control of each pulse, have kept routine marketed products limited; the concept remains an active goal of vaccine delivery research.

7.4 Mucosal delivery of vaccines

Most pathogens enter through mucosal surfaces (gut, respiratory tract, genital tract), so a vaccine applied at the mucosa can raise **secretory IgA** at the entry point plus systemic immunity, something injected vaccines do poorly.

- **Working examples:** oral polio vaccine, oral rotavirus vaccine, oral cholera and typhoid vaccines, and the intranasal live influenza vaccine (a fine spray, no needle).
- **Barriers:** dilution and clearance by mucus and cilia, enzymes and acid (for oral delivery the stomach is the first wall), tolerance, because the mucosal immune system is trained to ignore harmless food and commensal antigens, and the need for mucosal adjuvants that are safe on delicate surfaces.
- **Formulation answers:** mucoadhesive and particulate carriers that linger and are sampled by the M cells overlying Peyer's patches in the gut (the natural antigen sampling route), enteric protection for oral products, and dry powder or spray devices that deposit a controlled dose on the nasal mucosa.

7.5 Transdermal delivery of vaccines

Skin is immunologically rich: the epidermis carries Langerhans cells and the dermis carries dendritic cells, so antigen placed in the skin meets antigen presenting cells immediately. This is why intradermal

vaccination works at lower doses than intramuscular (dose sparing, used for rabies and some influenza and BCG practice, BCG being given intradermally by design).

- **Methods:** microneedle patches are the flagship technology: arrays of tiny solid, coated, hollow or dissolving needles that painlessly cross the stratum corneum and deposit antigen in the epidermis and upper dermis. Dissolving microneedle patches (sugar or polymer needles that melt into the skin) can be self applied, are stable without a deep cold chain in some designs, generate no sharp waste, and have shown strong responses in influenza and other trials.
- **Other skin routes:** needle free jet injectors, powder and particle bombardment devices, and topical application after barrier disruption (tape stripping, abrasion) in research settings.
- **Programme value:** painless, potentially self administered, dose sparing and sharps free delivery attacks the practical barriers of vaccination campaigns: fear of needles, trained staff, cold chain volume and waste disposal. That combination is why transdermal vaccine delivery closes this subject: it is delivery science applied to the largest preventive intervention in medicine.

Frequently Asked Questions

Q: What is the difference between sustained release and controlled release? Sustained release prolongs the release of drug over time and reduces dosing frequency, but the rate is not necessarily constant. Controlled release is stricter: the system releases the drug at a predetermined, ideally constant zero order rate, largely independent of the body environment, so plasma levels stay nearly flat.

Q: Which drugs are ideal candidates for SR and CR formulations? Drugs with a half life of about 2 to 8 hours, moderate solubility, adequate absorption from the whole gut, a dose that fits one unit (generally up to about 500 mg), a reasonable therapeutic index, and stability in gastrointestinal fluids. Very short or very long half life drugs, large dose drugs and drugs absorbed from one narrow gut region are poor candidates.

Q: How does an osmotic pump give zero order release, and how do the elementary and push pull designs differ? Water enters the tablet through a semipermeable cellulose acetate coat at a constant rate, drawn by the osmotic core. The pressure pushes drug solution out of a laser drilled orifice at the same constant rate while solid core material remains. Because water inflow is constant and independent of gut pH and motility, drug outflow is constant too: zero order. The elementary pump has a single core of drug with osmogen and works best for moderately soluble drugs. The push pull pump has two layers, a drug layer and a swelling push layer, so even poorly soluble drugs can be pushed out as a suspension at a constant rate; most modern once daily osmotic products use the push pull design.

Q: How do floating gastro-retentive systems work, and how are they evaluated? Floating systems keep their density below that of gastric fluid, either by trapped gas generated inside the form (effervescent type) or by a swollen gel that traps air. They are evaluated by floating lag time, total floating duration, swelling behaviour and in vitro release in simulated gastric fluid, with in vivo imaging such as gamma scintigraphy used to prove real retention.

Q: What is mucoadhesion and which polymers are most used for it? Mucoadhesion is the attachment of a dosage form to a mucosal surface, occurring by wetting and contact followed by interpenetration of polymer and mucin chains and formation of hydrogen bonds and other weak forces. Carbopol (polycarbophil) is the benchmark anionic polymer, chitosan is the main cationic one, and HPMC, sodium carboxymethyl cellulose and alginate are common blending partners.

Q: Why is buccal delivery said to avoid first pass metabolism? Blood from the buccal mucosa drains into the internal jugular vein and reaches the systemic circulation directly, without passing through the liver

first. The drug also escapes stomach acid and gut enzymes. This is why the buccal route suits potent drugs that are heavily metabolised on first pass or degraded in the gut.

Q: Why does so little of an eye drop reach inside the eye? The tear film holds only a few microlitres while a drop is 25 to 50 microlitres, so most of the dose spills or drains through the nasolacrimal duct within minutes, and the corneal layers then block much of what remains. Typically less than about 5 percent of the instilled dose enters the eye.

Q: What makes a drug suitable for transdermal delivery? It should be potent (milligram daily doses, ideally under 10 to 20 mg per day), small (molecular weight under about 500), moderately lipophilic (log P about 1 to 4), low melting, stable in the patch, and non irritating to skin. Only a small set of drugs meets all of these conditions, which is why the transdermal catalogue is short but valuable.

Q: Why are proteins and peptides almost always injected instead of given orally? In the gut they are hydrolysed by proteases within minutes, they are too large and polar to cross the intestinal membrane in useful amounts, and what little is absorbed faces further peptidase attack. Oral bioavailability is usually under 1 to 2 percent, so injection, increasingly in depot and carrier systems that protect and prolong the protein, remains the standard route.

Q: What is a single shot vaccine and how is it designed? It is a vaccine designed to replace a prime dose plus scheduled boosters with one administration. Part of the antigen is immediately available, and the rest is sealed in biodegradable polymer microsphere populations that erode at staggered times, releasing booster pulses weeks to months later. Antigen stability inside the degrading microspheres is the main technical challenge.