Principles of Immunization

Part 5: Infectious Diseases

KEY CLINICAL POINTS

1. Vaccines utilize inactivated or attenuated pathogens, or specific components (subunits/proteins), to induce protective immune responses.
2. Live attenuated vaccines provide robust immunity but are contraindicated in immunocompromised patients and during pregnancy.
3. Adjuvants (Alum, TLR agonists, Saponins) and delivery systems (LNPs) are critical for enhancing immunogenicity and stability.
4. The vaccine development continuum involves a multi-disciplinary path from preclinical research to clinical trials, regulatory approval, financing, and public health implementation.
5. Controlled Human Infection Models (CHIMs) are utilized when traditional clinical trials are not feasible.
6. ACIP determines U.S. vaccine recommendations; the VFC Program ensures access for children without insurance.
7. Passive immunity (e.g., monoclonal antibodies) provides rapid, short-term protection for high-risk populations.
8. Waning immunity necessitates booster doses (e.g., Tetanus every 10 years, annual Influenza).
9. mRNA platforms require lipid nanoparticles (LNPs) to ensure stability and effective delivery.
10. Clinical surveillance distinguishes between vaccine failure and failure to vaccinate.

1. DEFINITION & OVERVIEW

Vaccines are defined as inactivated or attenuated pathogens or components that stimulate a protective immune response.

- **Immunization Mechanisms:**
  - – Vaccination: Administration of vaccines to induce immunity against specific pathogens.
  - – Passive Immunity: Rapid protection via antibody transfer (e.g., monoclonal antibodies for RSV and SARS-CoV-2; maternal immunization for tetanus, influenza, and RSV).
- **Historical Context:**
  - – Origin: Edward Jenner's smallpox vaccine using cowpox material.
  - – Impact: Global vaccination programs have averted >37 million deaths (2000–2019), reducing mortality by 45%.

1.1 Vaccine Types and Mechanisms

Vaccines stimulate active immunity through antigen-specific responses:

- **Live attenuated vaccines**: Mimic natural infection; provide durable immunity but require caution in immunocompromised patients.

- **Inactivated vaccines**: Nonreplicating pathogens; may require adjuvants for robust response.
- **Subunit/protein-based vaccines**: Use purified antigens (e.g., hepatitis B, HPV).
- **mRNA vaccines**: Utilize lipid nanoparticle (LNP) delivery systems.

Passive immunity includes:

- **Monoclonal antibodies**: Used for RSV and SARS-CoV-2 in high-risk groups.
- **Maternal immunization**: Protects neonates against tetanus, influenza, and RSV.

1.2 Vaccine Formulations

Evolution of vaccine technologies:

- **Late 19th–mid 20th century**: Whole-cell typhoid, cholera; diphtheria/tetanus toxoids.
- **1950s–1980s**: Live attenuated (polio, measles) and conjugate vaccines (pneumococcal, Hib).
- **21st century**: Recombinant DNA (hepatitis B, HPV) and mRNA platforms (SARS-CoV-2).

Technological advancements:

- **Lipid nanoparticles**: Improved mRNA stability.
- **Structure-guided design**: Enhanced SARS-CoV-2 spike protein immunogenicity.
- **New adjuvants**: Matrix-M and QS-21 for malaria and shingles.

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2. EPIDEMIOLOGY

Vaccine development prioritizes diseases with high burden of illness:

- **Surveillance Systems**: (e.g., CDC) quantify disease incidence and at-risk populations.
- **Preparedness**: Pandemic threats (influenza, emerging pathogens) drive pre-emptive research.

2.1 Burden of Illness Studies

These studies guide public health priorities by measuring:

- Disease incidence and mortality.
- Economic impact.
- Identification of high-risk populations (elderly, immunocompromised).

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3. ETIOLOGY & PATHOPHYSIOLOGY

Immune responses to vaccines include:

- Serum antibodies, mucosal immunity, and memory cell formation.
- **Primary response**: Occurs weeks post-vaccination.
- **Secondary response (boosters)**: Occurs in days–weeks.

Live attenuated vaccines induce robust responses with fewer doses.

3.1 Vaccine Technologies (Table 128-1)

- **Live attenuated**: Weakened pathogens; durable immunity; large-scale manufacturing; requires caution in pregnant/immunocompromised patients.

- **Inactivated**: Nonreplicating; broad immune response; large-scale manufacturing.
- **Subunit/protein-based**: Specific parts of pathogen (e.g., influenza, acellular pertussis, shingles); low reactogenicity; may require multiple doses or adjuvants.
- **Conjugate**: Combines polysaccharide with protein carrier (e.g., pneumococcal, meningococcal, typhoid, Hib); strong response in all ages including infants.
- **Viral vector**: Nonpathogenic viruses deliver nucleic acid (e.g., Ebola, COVID-19); high manufacturing scalability; risk of immunity to vector.
- **mRNA**: Lipid nanoparticles deliver nucleic acid for in vivo production; rapid development/manufacturing.

Adjuvants:

- **Alum (Aluminum hydroxide/phosphate)**: Longest used; provides depot effect; used in HPV, hepatitis A, DTaP.
- **TLR agonists (MPL, CpG)**: Activate TLR to enhance antigen presentation; used in HPV (AS04), Shingles (MPL/QS-21), and Hepatitis B (CpG).
- **Saponin-based (Matrix-M, QS-21)**: Used for malaria and shingles.
- **Lipid nanoparticles (LNPs)**: Enhance lymphatic transport and antigen uptake for mRNA vaccines.

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4. CLINICAL FEATURES

Adverse events and reactogenicity:

- **Phase 1 trials**: Use dose-escalation with independent DSMCs.
- **Halting rules**: Trials are stopped for severe reactions (hospitalization) or multi-participant severe events.
- **Immunologic assessment**: Includes antibody titers and T-cell responses.

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5. DIFFERENTIAL DIAGNOSIS

Distinguishing vaccine failure from failure to vaccinate:

- **Vaccine Failure**: Failure of the vaccine to provide protection despite proper administration.
- **Failure to Vaccinate**: Lack of protection due to inadequate coverage or access.
- **Surveillance Role**: Identifies risk factors and gaps in efficacy; informs ACIP adjustments.

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6. INVESTIGATIONS & DIAGNOSIS

Immune response measurement:

- **Primary vs. Secondary**: Primary (weeks post-vaccination) vs. secondary boosters (days–weeks).
- **Serologic correlates of protection**: Antibody titers (ELISA, neutralization assays), mucosal IgA detection, T-cell proliferation assays, and memory B/T-cell enumeration.

6.1 Safety Monitoring

Safety monitoring systems include:

- **Phase 1–3 trials**: Data collection on safety and immunogenicity.

- **Postlicensure surveillance**: VAERS (Vaccine Safety Datalink) and VSD.
- **Real-time tracking**: FDA Adverse Event Reporting System.

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7. MANAGEMENT & TREATMENT

Vaccine development and implementation follow a multi-step progression:

1. **Preclinical Stage**: Antigen discovery, animal models, and study of pathogenesis/immune response.
2. **Clinical Studies**:
   - Phase 1: <100 volunteers; safety and immunogenicity.
   - Phase 2: Several hundred subjects; expanded safety and immunogenicity.
   - Phase 3: Thousands of participants; randomized placebo-controlled trials for efficacy.
3. **Approval**: Regulatory hurdles including political will, cost-effectiveness, and modeling.
4. **Financing**: Transition from approval to delivery.
5. **Delivery & Impact**: Logistics, overcoming vaccine inertia, and community acceptance.

7.1 Policy and Implementation

- **ACIP Guidelines**: Establish annual vaccination schedules for all age groups.
- **VFC Program**: Provides free vaccines for children without insurance.
- **Public/Private Coordination**: Collaboration with AAP, AAFP, and ACOG to address adult coverage challenges.

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8. PROGNOSIS & COMPLICATIONS

Long-term outcomes:

- **Waning Immunity**: Requires booster doses for sustained protection (e.g., Tetanus, pneumococcal).
- **Rare Adverse Events**: Monitored postlicensure via VAERS and VSD.

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9. SPECIAL CONSIDERATIONS

Special populations:

- **Pregnancy**:
  - Tdap: Administered at 27–36 weeks.
  - Influenza: Inactivated vaccine during flu season.
  - RSV: Monoclonal antibodies for high-risk infants.
- **Immunocompromised Patients**:
  - Contraindication: Avoid live attenuated vaccines (e.g., MMR, varicella).
  - Recommendation: Use inactivated vaccines (e.g., pneumococcal, influenza).
  - Monitoring: Watch for vaccine failure due to impaired immunity.

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10. KEY PEARLS & CLINICAL TRAPS

Critical insights:

- **mRNA Stability**: Requires Lipid Nanoparticles (LNPs) for effective delivery.
- **Adjuvant Selection**: Alum is standard; TLR agonists and Saponins are used for specific pathogens like HPV, Shingles, and Malaria.
- **Vaccine Development Continuum**:

1. Burden of disease assessment
2. Antigen discovery/preclinical studies
3. Phase 1–3 trials
4. Licensure/policy-making
5. Implementation/monitoring

- **Policy Infrastructure (Figure 128-3)**:

1. Vaccine development and testing → Submission to FDA for Biologics License Application.
2. FDA licensure (advised by VRBPAC).
3. Decision Pathways:
   – CDC Track: ACIP advises → CDC consideration → Publication in *MMWR*.
   – ACP Track: Board of Regents & Adult Immunization Initiative Physician Advisory Board advise → Publication in *Annals*.
4. Implementation:
   – Public Sector: Insurance or Medicare coverage.
   – Private Sector: Uptake and financing.

REFERENCE TABLES

TABLE 128-1
Categories and Characteristics of Approved Vaccines and Adjuvants TECHNOLOGY Live attenuated

VACCINES				
TECHNOLOGY	DESCRIPTION	EXAMPLES OF APPROVED VACCINES	ADVANTAGES	DISADVANTAGES
Live attenuated	Weakened or attenuated form of the pathogen that causes disease	Measles, mumps, rubella, varicella, oral poliomyelitis, nasal influenza vaccine, oral rotavirus	Mimics natural infection Effective priming with durable immunity Large-scale manufacturing capabilities Single or two doses often sufficient	Difficult to reach desired level of attenuation Safety concerns for certain populations (e.g., pregnant women, immunocompromised patients) Stability

	Pathogens or toxins rendered nonreplicating through heat or chemical processes (may be entire pathogen or parts of it)	Inactivated poliomyelitis, hepatitis A, whole-cell pertussis, tetanus and diphtheria toxoids	Induces broad immune response to multiple antigens Large-scale manufacturing capabilities	
Purified protein-based (split or subunit)	Specific parts of the pathogen are produced in culture	Influenza, acellular pertussis, recombinant shingles	Highly specific immune response Noninfectious Low reactogenicity Ease of production	Multiple doses may be needed May require adjuvant Limited cross-protective immunity
	Type of subunit vaccine that combines a polysaccharide antigen with a protein carrier to improve immune responses	Pneumococcal, meningococcal, typhoid, Hib	Conjugate protein may also provide immunity (e.g., tetanus) Strong immune responses in all ages, including infants	
Virus-like particles	One or more proteins arranged to closely resemble viruses	Hepatitis B, HPV	Broad and robust immunity Noninfectious	Technically difficult to produce Lower stability
	Replicating, nonpathogenic viruses deliver nucleic acid to host for in vivo production of antigen	Vesicular stomatitis virus–based Ebola vaccine	Induces broad immune response High manufacturing scalability	
Nonreplicating viral vector	Replication-deficient nonpathogenic viruses deliver nucleic acid to host for in vivo production of antigen	Chimp adenovirus–based COVID-19 vaccine	Induces broad immune response High manufacturing scalability	Immunity to vector may dampen immune response

	Lipid nanoparticles deliver nucleic acid to host for in vivo production of antigen	COVID-19 mRNA vaccines	Rapid development and manufacturing timelines Effective and safe for majority of population
ADJUVANTS			
TECHNOLOGY	EXAMPLES	CURRENT USE	MECHANISM OF ACTION
Alum	Aluminum hydroxide or aluminum phosphate	Multiple vaccines—e.g., HPV, hepatitis A, DTaP	Possible depot effect; increases antibody production
	AS03, MF59	Influenza	
Toll-like receptor (TLR) agonists	Monophosphoryl lipid A (MPL) Cytosine-phosphate-guanine (CpG)	HPV (AS04—MPL and alum) Shingles (MPL and QS21) Hepatitis B (CPG)	Activates TLR to enhance antigen presentation and enhance adaptive immune responses
	QS-21, Matrix-M	Malaria vaccines (MPL, QS21, and Matrix-M) COVID-19 (Matrix M)	
Delivery platforms	Lipid nanoparticle (LNP)	COVID-19 mRNA vaccines	Improved lymphatic transport enhances antigen uptake and presentation