From Vaccine to Vaccination: It takes a Village

Association for Clinical and Translational Science
Washington, DC
April 10, 2014

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Deputy Assistant Secretary for Health
Director, National Vaccine Program Office
Department of Health and Human Services
• RESEARCH
• EDUCATION
• ADVOCACY
• MENTORING
ACTS Research Focus:

- Improve team science
- Integrate multiple disciplines:
  - Basic discovery
  - Patient oriented and human subject clinical research
  - Population based and policy research
- **GOAL**: Improve the efficiency with which health needs inform research and new therapies reach the public

http://www.actscience.org/
Vaccine and Immunization Framework

Surveillance
Research
Testing and Development
Licensing
Recommendations and Use
Measuring Impact
Scientific Discovery and Vaccine Research and Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1796</td>
<td>Smallpox</td>
</tr>
<tr>
<td>1800-1920</td>
<td>Rabies, Typhoid, Cholera, Plague, Diphtheria toxin</td>
</tr>
<tr>
<td>1850</td>
<td>Birth of Immunology</td>
</tr>
<tr>
<td>1900-1920</td>
<td>Germ theory of disease accepted</td>
</tr>
<tr>
<td>1920-1960</td>
<td>Diphtheria toxoid, BCG (Tuberculosis), Pertussis, Tetanus toxoid, Yellow Fever, Influenza, Polio</td>
</tr>
<tr>
<td>1950</td>
<td>Tissue culture</td>
</tr>
<tr>
<td>1990-2003</td>
<td>Novel delivery strategies, adjuvants</td>
</tr>
<tr>
<td>2003</td>
<td>New Biotechnology MAb, rDNA</td>
</tr>
<tr>
<td></td>
<td>Pneumococcal conjugate cold-adapted nasal flu vaccine</td>
</tr>
<tr>
<td></td>
<td>Japanese encephalitis Vi Typhoid</td>
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</table>

Cumulative Total
US Recommended Schedule for Persons Aged 0-6 Years (1982)

<table>
<thead>
<tr>
<th></th>
<th>2 mo</th>
<th>4 mo</th>
<th>6 mo</th>
<th>12 mo</th>
<th>15 mo</th>
<th>18 mo</th>
<th>4 – 6 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diphtheria, Tetanus, Pertussis</strong></td>
<td>DTP</td>
<td>DTP</td>
<td>DTP</td>
<td>DTP</td>
<td>DTP</td>
<td>DTP</td>
<td>DTP</td>
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<tr>
<td><strong>Polio</strong></td>
<td>OPV</td>
<td>OPV</td>
<td>OPV</td>
<td>OPV</td>
<td></td>
<td></td>
<td>OPV</td>
</tr>
<tr>
<td><strong>Measles, Mumps, Rubella</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MMR</td>
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</table>
### TABLE 1. Recommended childhood immunization schedule* — United States, January 1995

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>2 Months</th>
<th>4 Months</th>
<th>6 Months</th>
<th>12† Months</th>
<th>15 Months</th>
<th>18 Months</th>
<th>4 - 6 Years</th>
<th>11-12 Years</th>
<th>14-16 Years</th>
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<tr>
<td>Hepatitis B §</td>
<td>HB-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, Tetanus, Pertussis*</td>
<td>DTP</td>
<td>DTP</td>
<td>DTP</td>
<td></td>
<td>DTP or DTaP at ≥15 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. influenzae type b **</td>
<td>Hib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poliovirus</td>
<td>OPV</td>
<td>OPV</td>
<td>OPV</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Measles, Mumps, Rubella †</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

*For persons aged 0-6 years.

†Age 12 months should also receive inactivated poliovirus vaccine (IPV) as part of the routine 12-month visit. Monthly doses of Hib should be given at ages 2, 4, and 6 months. DTaP should be given instead of DTP at age 6 months.

‡MMR should be given as a single dose at age 15 or 16 months. If MMR is not given at age 15 or 16 months, two doses of MMR (separated by at least 1 month) should be given at ages 15 or 16 months and ≥4 years.
US Recommended Schedule for Persons Aged 0-18 Years (2014)

This schedule includes recommendations for all children and specific high-risk groups. Any dose not recommended at the appropriate age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm) or by telephone (800-CDC-INFO (800-232-4636)).

NOTE: The above recommendations must be read along with the footnotes of this schedule.
National Vaccine Program
Responsibilities Title XXI Public
Health Service Act

- Vaccine Research
- Vaccine Development
- Safety and efficacy testing of vaccines
- Licensing of vaccine manufacturers and vaccines
- Production and procurement of vaccines
- Distribution and use of vaccines
- Evaluating the need for, the effectiveness, and adverse effects of vaccines and immunization activities
- Coordinating governmental and non-governmental activities
- Funding of federal agencies
The Nation’s Vaccine and Immunization Enterprise:
A system perspective

Basic Science/Discovery

Disease Surveillance

Recognition of public health priorities

Vaccine Research

Vaccine Development

Vaccine Licensure

Vaccine Manufacture

Vaccine Sales/Purchase

Vaccine Distribution

Vaccination (Adult, Adolescent and Childhood)

Adverse Event Monitoring

Vaccine Coverage Surveillance

Vaccine Effectiveness

Access/Payment for Vaccination/Reimbursement

Development of vaccine recommendations

Communication and Education Strategies

Attitudes about vaccination

Vaccine Coverage Surveillance

High Vaccination Rates

Population health protection against infectious disease in the U.S. and globally

Reduced morbidity and mortality from infectious disease in the U.S. and globally

Vaccine Injury Compensation

Recognition of public health priorities

Translational research for diffusion of innovation
The Nation’s Vaccine and Immunization Enterprise: A system perspective

- Basic Science/Discovery
  - Recognition of public health priorities
  - Vaccine Research
  - Vaccine Development
  - Vaccine Licensure
  - Vaccine Manufacture
  - Vaccine Sales/Purchase
  - Vaccine Distribution
- Attitudes about vaccination
- Communication and Education Strategies
- Develop vaccine recommendations
- Access/Payment for Vaccination/Reimbursement
- Vaccination (Adult, Adolescent and Childhood)
- Adverse Event Monitoring
- Vaccine Coverage Surveillance
- Vaccine Effectiveness
- High Vaccination Rates
  - Population health protection against infectious disease in the U.S. and Globally
  - Reduced Morbidity and Mortality from infectious disease in the U.S. and Globally
- Vaccine Injury Compensation

- Disease Surveillance
  - Translational research for diffusion of innovation
National Institutes of Health

Mission:

• Seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability.

• Foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health.
• Process development and manufacturing
• Formulation, stability, fill/finish
• Assay development
• In vivo immunogenicity
• Preclinical and clinical services to facilitate product development
• Funding opportunities
Preclinical Development Services

Product Development Pathway

Basic Research
- Hypothesis Development and Testing

Preclinical Development
- Discovery
- IDE- and IND-Enabling Activities

Clinical Evaluation
- Trials

Research Tools and Technologies

- Animal Models of Infectious Diseases
- *In vitro* Assessment for Antimicrobial Activity
- Therapeutics Development Services
- Vaccine Development Services
- Assay Development

- Diagnostics
- Vaccines
- Therapeutics
The Jordan Report: Accelerated Development of Vaccines 2012
• Facilitating other translational research activities supported by NIH.
• Complementing research conducted in the private sector.
• Reinforcing NIH’s commitment to basic research.
Centers for Disease Control and Prevention

• Monitor health
  – Surveillance
  – Detect and investigate health problems
• Conduct research to enhance prevention
• Develop sound public health policies
• Implement prevention strategies
• Promote healthy behaviors
Centers for Disease Control and Prevention: Vaccine and Immunization Focus

- Disease surveillance: Domestic/Global
- Vaccine coverage
  - National Immunization Survey
  - Vaccine efficacy/effectiveness
  - Vaccine Safety

- ACIP: Advisory Committee on Immunization Practices
  - Develops recommendations on how to use vaccines to control diseases in the United States.
Regulatory Science: Vaccine Focus

- Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease
- Considerations for Plasmid DNA Vaccines for Infectious Disease Indications
- Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials
- Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines
- Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines
- Development of Preventive HIV Vaccines for Use in Pediatric Populations
- Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications
- Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing and Clinical Studies
Mission: Develop and procure medical countermeasures that address the public health and medical consequences of chemical, biological, radiological, and nuclear (CBRN) accidents, incidents and attacks, pandemic influenza, and emerging infectious diseases
Product Development Pipeline

**PHASES**
- Discovery
- Preclinical Development
- Phase I
- Phase II
- Phase III
- Licensure
- Production & Delivery

**PROBABILITY OF SUCCESS TO LICENSURE**
- 1-3%: 5
- 5-17%: 15
- 10-25%: 18
- 18-35%: 45
- 45-70%: 90

**FUNDING**
- NIH ($11.8B)
- BARDA ($540M)
- Project BioShield ($5.6B)

**Valley of Death**

**Licensed Product**
Expand capabilities and increase engagement with end-users.

ENGAGE with end-users to prioritize vaccines and innovations according to perceived demand and added value.

ESTABLISH platforms for exchange of information on immunization research and consensus building.

BUILD more capacity and human resources in low- and middle-income countries to conduct research and development and operational research.

INCREASE networking among research centres for efficient building of partnerships among the institutions of high-, middle- and low-income countries.

PROMOTE collaboration between traditional research disciplines and scientists from disciplines not previously engaged in vaccine research.

Improve programme efficiencies and increase coverage and impact.

RESEARCH the use of more effective information through modern communication technologies.

CONDUCT representative epidemiological, immunological, social and operational studies and investigations of vaccine impact to guide health economics analysis.

PERFORM operational research on improved delivery approaches for life-course immunization, and vaccination in humanitarian emergencies, so-called fragile States and countries in and emerging from conflict.

PERFORM research on interference effects and optimum delivery schedules.

PERFORM research to develop improved diagnostic tools for conducting surveillance in low-income countries.

PROMOTE greater access to technology, expertise and intellectual property for adjuvants and their formulation into vaccines.

DEVELOP non-syringe delivery mechanisms and vaccine packaging that best suit the needs and constraints of national programmes.

DEVELOP thermostable rotavirus and measles vaccines.

DEVELOP new bioprocessing and manufacturing technologies.

DEVELOP a global, regulatory science research agenda.

ADOPT best practices in portfolio and partnership management for research and development.

Enable the development of new vaccines.

RESEARCH on the fundamentals of innate and adaptive immune responses, particularly in humans.

RESEARCH on immunological and molecular characteristics of microbes.

IMPROVE understanding of the extent and causes of variation in pathogens and human population responses to vaccines.
**Research**
- Fundamentals of innate and adaptive immunity
- Immunological and molecular characteristics of microbes
- Improved understanding of variation of pathogens and human responses to vaccines
- More effective information/communication

**Develop**
- Thermostable vaccines
- New bioprocessing and manufacturing technologies
- Non-syringe delivery mechanisms
- Vaccine presentations that fit needs and constraints of national programs
National Vaccine Program Office

2010 National Vaccine Plan

Protecting the Nation's Health through Immunization
2010 National Vaccine Plan

Goals:

1. Develop new and improved vaccines

2. Enhance the vaccine safety system

3. Support communications to enhance informed vaccine decision-making

4. Ensure a stable supply of recommended vaccines and achieve better use of existing vaccines to prevent disease, disability and death in the United States

5. Increase global prevention of death and disease through safe and effective vaccination*
2010 National Vaccine Plan

Goals:

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3. Support communications to enhance informed vaccine decision-making

4. Ensure a stable supply of recommended vaccines and achieve better use of existing vaccines to prevent disease, disability and death in the United States

5. Increase global prevention of death and disease through safe and effective vaccination*
National Vaccine Plan: Develop New and Improved Vaccines (1)

- Prioritize new vaccine targets of domestic and global public health importance
- Support research to develop and manufacture new vaccine candidates and improve current vaccines to prevent infectious diseases
- Support research on novel and improved vaccine delivery methods
National Vaccine Plan: Develop New and Improved Vaccines (2)

- Increase understanding of the host immune system
- Support product development, evaluation, and production techniques of vaccine candidates and the scientific tools needed for their evaluation
- Improve the tools, standards, and approaches to assess the safety, efficacy, and quality of vaccines
Vaccine Development Priorities

- HIV
- TB
- Malaria
- Universal Influenza
A framework and proof of concept to account for various factors influencing vaccine prioritization: demographic, economic, health, scientific, business, programmatic, social, policy factors and public concerns.

Institute of Medicine (2013)
# Desired Vaccine Characteristics

<table>
<thead>
<tr>
<th>Health Considerations</th>
<th>Economic Considerations</th>
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<tbody>
<tr>
<td>• Premature Deaths Averted Per Year</td>
<td>• One-Time Costs</td>
</tr>
<tr>
<td>• Incident Cases Prevented Per Year</td>
<td>• Annual Net Direct Costs (Savings) of Vaccine Use</td>
</tr>
<tr>
<td>• QALYs Gained or DALYs Averted</td>
<td>• Annual Net Workforce Productivity Gained</td>
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<tr>
<td></td>
<td>• Cost-Effectiveness</td>
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<td></td>
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<tr>
<td>Demographic Considerations</td>
<td>Demographic Considerations</td>
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<tr>
<td>• Benefits Infants and Children</td>
<td>• Benefits Women</td>
</tr>
<tr>
<td>• Benefits Women</td>
<td>• Benefits Socioeconomically Disadvantaged</td>
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<tr>
<td>• Benefits Military Personnel</td>
<td>• Benefits Other Priority Population</td>
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<tr>
<td>Public Concerns</td>
<td>Public Concerns</td>
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<tr>
<td>• Availability of Alternative Public Health Measures</td>
<td>• Potential Complications Due to Vaccines</td>
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<tr>
<td>• Potential Complications Due to Vaccines</td>
<td>• Disease Raises Fear and Stigma in the Public</td>
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<tr>
<td>• Disease Raises Fear and Stigma in the Public</td>
<td>• Serious Pandemic Potential</td>
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<tr>
<td>Scientific and Business Considerations</td>
<td>Scientific and Business Considerations</td>
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<tr>
<td>• Likelihood of Financial Profitability for the Manufacturer</td>
<td>• Likelihood of Successful Licensure in 10 Years</td>
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<td>• Likelihood of Successful Licensure in 10 Years</td>
<td>• Demonstrates New Production Platforms</td>
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<td>• Demonstrates New Production Platforms</td>
<td>• Existing or Adaptable Manufacturing Techniques</td>
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<td>• Existing or Adaptable Manufacturing Techniques</td>
<td>• Potential Litigation Barriers Beyond Usual</td>
</tr>
<tr>
<td>• Potential Litigation Barriers Beyond Usual</td>
<td>• Interests from NGOs and Philanthropic Organizations</td>
</tr>
<tr>
<td>• Interests from NGOs and Philanthropic Organizations</td>
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<td>Programmatic Considerations</td>
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<tr>
<td>• Potential to Improve Delivery Methods</td>
<td>• Fits into Existing Immunization Schedules</td>
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<tr>
<td>• Fits into Existing Immunization Schedules</td>
<td>• Reduces Challenges Relating to Cold-Chain Requirements</td>
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<td>Intangible Values</td>
<td>Intangible Values</td>
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<tr>
<td>• Eradication or Elimination of the Disease</td>
<td>• Vaccine Raises Public Health Awareness</td>
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<tr>
<td>Policy Considerations</td>
<td>Policy Considerations</td>
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<tr>
<td>• Special Interest for National Security, Preparedness, and Response</td>
<td>• Advances Nation’s Foreign Policy Goals</td>
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</table>
From Vaccine to Vaccination: It takes a Village

or...

Case Studies in Team R&D
Protection against meningococcal meningitis has come a long way, due in large part to advances in vaccines to help protect against some of the most dangerous strains. Click on a date to navigate the major milestones in the history of meningococcal meningitis.

1805

Swiss physician Gaspard Vieusseux first describes meningococcal disease, following an epidemic in Geneva, Switzerland.
HISTORY OF MENINGOCOCCAL MENINGITIS

Protection against meningococcal meningitis has come a long way, due in large part to advances in vaccines to help protect against some of the most dangerous strains. Click on a date to navigate the major milestones in the history of meningococcal meningitis.

1887

Austrian pathologist and bacteriologist Anton Weichselbaum discovers Neisseria meningitidis, the bacterium that causes meningococcal disease, in patients affected by meningitis.¹
HISTORY OF MENINGOCOCCAL MENINGITIS

Protection against meningococcal meningitis has come a long way, due in large part to advances in vaccines to help protect against some of the most dangerous strains. Click on a date to navigate the major milestones in the history of meningococcal meningitis.

1900-10

At the turn of the 20th century, 75% to 80% of people infected with meningococcal meningitis die from the disease.²
HISTORY OF MENINGOCOCCAL MENINGITIS

Protection against meningococcal meningitis has come a long way, due in large part to advances in vaccines to help protect against some of the most dangerous strains. Click on a date to navigate the major milestones in the history of meningococcal meningitis.

1913

American scientist Simon Flexner develops an antimeningococcal serum that is shown to decrease mortality in people with meningococcal meningitis.
HISTORY OF MENINGOCOCCAL MENINGITIS

Protection against meningococcal meningitis has come a long way, due in large part to advances in vaccines to help protect against some of the most dangerous strains. Click on a date to navigate the major milestones in the history of meningococcal meningitis.

1969

A team of military doctors at the Walter Reed Army Institute of Research led by Emil C. Gotschlich develop a method for purifying meningococcal polysaccharides that were safe and produced an immune response, which formed the basis of the currently licensed bivalent (A and C) and quadrivalent (A, C, W-135, and Y) polysaccharide vaccines.
HISTORY OF MENINGOCOCCAL MENINGITIS

Protection against meningococcal meningitis has come a long way, due in large part to advances in vaccines to help protect against some of the most dangerous strains. Click on a date to navigate the major milestones in the history of meningococcal meningitis.

1974

The first polysaccharide vaccine for meningococcal meningitis is approved, but it only protects against 1 of the 5 serogroups.³
**HISTORY OF MениNGOCOCCAL MениNGITIS**

Protection against meningococcal meningitis has come a long way, due in large part to advances in vaccines to help protect against some of the most dangerous strains. Click on a date to navigate the major milestones in the history of meningococcal meningitis.


**1978**

The first meningococcal disease vaccine to help protect against 4 of the 5 major serogroups of meningococcal bacteria is licensed in the United States.³
HISTORY OF MENINGOCOCCAL MENINGITIS

Protection against meningococcal meningitis has come a long way, due in large part to advances in vaccines to help protect against some of the most dangerous strains. Click on a date to navigate the major milestones in the history of meningococcal meningitis.

### 2005-10

The FDA licenses additional meningococcal disease vaccines, called meningococcal conjugate vaccines, to help protect against 4 of the 5 major disease-causing serogroups, A, C, Y, and W-135.
CHEMO-IMMUNOLOGICAL STUDIES ON CONJUGATED CARBOHYDRATE-PROTEINS

I. THE SYNTHESIS OF \( p \)-AMINOPHENOL \( \beta \)-GLUCOSIDE, \( p \)-AMINOPHENOL \( \beta \)-GALACTOSIDE, AND THEIR COUPLING WITH SERUM GLOBULIN

By Walther F. Goebel, Ph.D., and Oswald T. Avery, M.D.

(From the Hospital of The Rockefeller Institute for Medical Research)

(Received for publication, June 24, 1929)

The problems of the relationship between chemical constitution, physiological effect and biological specificity, which found their origin in the study of the active principles of certain natural drugs, have become so absorbing and so embracing that they have attracted and held the interest of the chemist, the pharmacologist, and the immunologist alike. The question of protein specificity (1), and that of whether it is possible to change specificity by altering the protein molecule through chemical means, have, in particular, engaged the minds of many investigators. On the other hand, the rôle which carbohydrates play in the phenomena of immunity has only recently been disclosed, despite the fact that the presence of these substances in
Meningitis ABCs...and beyond
Demand for Meningitis Vaccines
More than 151 million people protected from meningitis in sub-Saharan Africa

More than 48.3 million individuals received one dose of MenAfriVac®, the group A meningococcal conjugate vaccine developed through the Meningitis Vaccine Project, in 2013, bringing the total number of vaccinees to 731 million across 28 countries in Africa. This record number of people vaccinated reflects the success of the five-year campaign to eliminate epidemic meningitis as a public health problem in sub-Saharan Africa.

NEWS AND EVENTS

Study shows dramatic impact of MenAfriVac® in sub-Saharan Africa
Read the September 12, 2013, article in The Lancet.

Number of meningitis cases in Africa’s meningitis belt at the lowest level in ten years
The decrease is thought to be due to the introduction of MenAfriVac®, the meningococcal A conjugate vaccine developed by the MVP.
Read the WHO report of June 6, 2013.
Listen to Channel Africa Radio's interview with Dr. Marie-Pierre Préziosi.

Meningococcal disease in the African meningitis belt, 2012
Read the report.

MenAfriVac vaccination campaign in Chad
Read the MVP statement of January 10, 2013.
MenAfriVac® breaks the cold chain barrier!

19 February 2014—A study published online today in the journal Vaccine shows that removing the pioneering vaccine from constant refrigeration is not only safe but could extend vaccination coverage to the remotest regions in sub-Saharan Africa.
Princeton starts offering meningitis B vaccination to students

By Elizabeth Landau, CNN
updated 9:25 AM EST, Mon December 9, 2013

(CNN) -- A vaccine not licensed for use in the United States will be offered to thousands of Princeton University students beginning Monday, after a string of meningitis B cases at the college this year.
KISS ME
I'M VACCINATED
The Challenge of Meningococcal B Vaccine Development

- Capsular vaccine poorly immunogenic
- Structural homology between the B polysaccharide of the capsule and human tissue
- Serogroup B strains are highly diverse
  - >80 different outer membrane vesicle (OMV) types
Reverse Vaccinology: Developing Vaccines in the Era of Genomics

Alessandro Sette1 and Rino Rappuoli2,*
1La Jolla Institute for Allergy and Immunology, San Diego, CA 92130, USA
2Novartis Vaccines, 53100 Siena, Italy
*Correspondence: rino.rappuoli@novartis.com
DOI 10.1016/j.immuni.2010.09.017

The sequence of microbial genomes made all potential antigens of each pathogen available for vaccine development. This increased by orders of magnitude potential vaccine targets in bacteria, parasites, and large viruses and revealed virtually all their CD4+ and CD8+ T cell epitopes. The genomic information was first used for the development of a vaccine against serogroup B meningococcus, and it is now being used for several other bacterial vaccines. In this review, we will first summarize the impact that genome sequencing has had on vaccine development, and then we will analyze how the genomic information can help further our understanding of immunity to infection or vaccination and lead to the design of better vaccines by diving into the world of T cell immunity.
Reverse Vaccinology: Developing Vaccines in the Era of Genomics

1. Whole genome sequences may identify potential protein antigens.
2. Facilitates rapid identification of promising vaccine targets.

Microbial genomes made all potential antigens of each pathogen available for vaccine design. This increased by orders of magnitude potential vaccine targets in bacteria, parasites, and viruses and revealed virtually all their CD4+ and CD8+ T cell epitopes. The genomic information was first used for the development of a vaccine against serogroup B meningococcus, and it is now being used for several other bacterial vaccines. In this review, we will first summarize the impact that genome sequencing has had on vaccine development, and then we will analyze how the genomic information can help further our understanding of immunity to infection or vaccination and lead to the design of better vaccines by digging into the world of T cell immunity.
## Immunogenic Targets

<table>
<thead>
<tr>
<th>fHbp: factor H binding protein</th>
<th>NHBA: neisseria heparin-binding antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binds factor H, which enables bacterial survival in the blood(^1,2)</td>
<td>Binds heparin, which may promote bacterial survival in the blood(^7)</td>
</tr>
<tr>
<td></td>
<td>Present in virtually all strains(^6,7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NadA: neisserial adhesin A</th>
<th>NZ PorA P1.4: porin A</th>
</tr>
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<tbody>
<tr>
<td>Promotes adherence to and invasion of human epithelial cells(^3,5)</td>
<td>Major outer membrane vesicle protein—induces strain-specific bactericidal response(^8)</td>
</tr>
<tr>
<td>May be important for colonisation(^4)</td>
<td></td>
</tr>
</tbody>
</table>
Meningitis B vaccine rejected by UK
Joint Committee on Vaccination and Immunisation says there is not enough evidence to justify routine jabs with Bexsero

Sarah Boseley, health editor
theguardian.com, Wednesday 24 July 2013 07.24 EDT
Jump to comments (93)
UK experts back meningitis B jab

By Caroline Parkinson
Health editor, BBC News website

The vaccine will be given at two, four and 12 months

A vaccine that protects against a deadly form of meningitis is set to be introduced in the UK.

The Joint Committee on Vaccination and Immunisation (JCVI), which has recommended the vaccine for children, said it would prevent about 100 deaths a year.
FDA Grants Breakthrough Therapy Designation To Novartis' Meningitis B Vaccine

Novartis AG in Basel announced early this morning that the U.S. Food and Drug Administration has granted Breakthrough Therapy designation — a rapid development track — for potential approval of Bexsero®, their innovative vaccine against type B meningococcal meningitis.

Bexsero® is a four-component vaccine (called 4CMenB) that’s currently approved in Europe, Canada and Australia. It was deployed last year for outbreaks at Princeton University and the University of California, Santa Barbara, under an Investigational New Drug application to combat meningitis B cases.

This vaccine prevents a particular form of meningococcal disease caused by a bacterium called Neisseria meningitidis serogroup B, or MenB, and is currently not covered by existing vaccines required of entering U.S. college
Natural history of HPV infection

- Normal Cervix
- HPV Infection
- Precursor Lesion
- Invasive Lesion

Progression:
- Clearance
- Regression
Shope’s Horned Rabbit
Shope’s Horned Rabbit

Jackalope
Number of cancers caused by HPV worldwide/year

- Cervix: 530,000
- Vagina: 9,000 (Male: 4,000, Female: 5,000)
- Penis: 11,000
- Vulva: 12,000
- Oropharynx: 17,000 (Male: 12,000, Female: 5,000)
- Anus: 11,000 (Male: 4,000, Female: 7,000)
- Female: 5,400
- Male: 5,000
Numbers of U.S. Cancers and Genital Warts Attributed to HPV Infections

- Penis: 400
- Vagina: 500
- Juvenile-Onset RRP: 820
- Vulva: 1,600
- Anus: 1,600 + 2,900 = 4,500
- Oropharynx: 5,900 + 1,500 = 7,400
- Cervix: 11,500
- Genital Warts: 160,000 + 180,000 = 340,000

- Male
- Female
- Includes Males and Females
GOD'S GIFT TO WOMEN
Why Australian of the Year Professor Ian Frazer, a loving husband and father of three, has female admirers across the globe.
Accelerating HPV Vaccine Uptake:

Urgency for Action to Prevent Cancer

A Report to the President of the United States from
The President’s Cancer Panel

February 2014
Accelerating HPV Vaccine Uptake:
Urgency for Action to Prevent Cancer

A Report to the President of the United States
from
The President’s Cancer Panel

February 2014
# Barriers to HPV vaccination

<table>
<thead>
<tr>
<th>Healthcare Professionals</th>
<th>Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent’s attitudes and concerns</td>
<td>Not receiving a recommendation from their provider</td>
</tr>
<tr>
<td>Financial concerns</td>
<td>Need more information about the vaccine</td>
</tr>
<tr>
<td>Knowledge gaps</td>
<td>Believe child is too young for the vaccine</td>
</tr>
<tr>
<td>Inadequate insurance coverage and reimbursement</td>
<td>Concerns about vaccine safety, adverse effects, “new vaccine”</td>
</tr>
<tr>
<td>Preference for vaccinating older vs younger adolescents</td>
<td>Cost of the vaccine</td>
</tr>
<tr>
<td>Preference for vaccinating girls vs boys</td>
<td>Concerns about finding a clinic that offers the vaccine</td>
</tr>
</tbody>
</table>

Recommendations

1. Reduced Missed Clinical Opportunities to Recommend and Administer HPV Vaccines
2. Increase Parents’, Caregivers’ and Adolescents’ Acceptance of HPV Vaccines
3. Maximize Access to HPV Vaccination Services
4. Promote Global Vaccine Uptake
5. High Priority Research to Advance Prevention of HPV-associated Cancers
From Vaccine to Vaccination:
It Takes a Village

Vaccine Research
Vaccine Manufacture
Vaccine Sales/Purchase
Vaccine Distribution

Communication and Education Strategies
Develop vaccine recommendations
Access/Payment for Vaccination/Reimbursement

Attitudes about vaccination

Vaccination (Adult, Adolescent and Childhood)

Adverse Event Monitoring

Vaccine Effectiveness
Vaccine Coverage Surveillance

High Vaccination Rates
Population health protection against infectious disease in the U.S. and Globally
Reduced Morbidity and Mortality from infectious disease in the U.S. and Globally

Vaccine Injury Compensation

Basic Science/Discovery
Recognition of public health priorities

Disease Surveillance
Translational research for diffusion of innovation
**High-Priority Research Areas**

- Investigate more convenient dosing schedules for current vaccines.
- Develop next-generation vaccines that provide broader protection and/or are easier to store and administer.
- Explain the natural history of oropharyngeal HPV infections.
- Develop more effective ways to communicate about HPV-associated diseases and HPV vaccines.
- Determine how best to integrate HPV vaccination with cervical cancer screening.
From Vaccine to Vaccination: It Takes a Village

- **Basic Science/Discovery**
  - Recognition of public health priorities

- **Disease Surveillance**
  - Vaccine Research
  - Vaccine Development
  - Vaccine Licensure
  - Vaccine Manufacture
  - Vaccine Distribution
  - Vaccine Sales/Purchase

- **Translational Research**
  - Vaccine Refrigeration
  - Vaccine Effectiveness
  - Vaccine Coverage Surveillance

- **Communication and Education Strategies**
  - Attitudes about vaccination

- **Access/Payment for Vaccination/Reimbursement**
  - Adverse Event Monitoring

- **Vaccination (Adult, Adolescent and Childhood)**

- **Vaccine Coverage Surveillance**
  - High Vaccination Rates
  - Population health protection against infectious disease in the U.S. and globally
  - Reduced morbidity and mortality from infectious disease in the U.S. and globally

- **Vaccine Injury Compensation**

- **Vaccine Licensure**
Extra Slides
2010 National Vaccine Plan

Goals:

1. Develop new and improved vaccines

2. Enhance the vaccine safety system

3. Support communications to enhance informed vaccine decision-making

4. Ensure a stable supply of recommended vaccines and achieve better use of existing vaccines to prevent disease, disability and death in the United States

5. Increase global prevention of death and disease through safe and effective vaccination*
“The Cow Pock – or – the Wonderful Effects of the New Inoculation!”
J. Gillray, 1802
Goldman Sachs Gets Swine Flu Vaccine

When most people saw the headline 'GOLDMAN SACHS GETS SWINE FLU VACCINE' they were super happy ...until they read the word 'vaccine'
Evolution of an Immunization Program (and Prominence of Vaccine Safety)

1. Prevaccine
2. Increasing Coverage
3. Loss of Confidence
4. Resumption of Confidence
5. Eradication

- Incidence
- Vaccination Coverage
- Disease
- Adverse Events
- Outbreak
- Eradication

More than 25% of Parents Delay Some or All Vaccines
National Immunization Survey 2009

The reasons:

- 27% said too many shots were recommended
- 26% questioned whether vaccines really worked
- 25% worried that vaccines might cause autism
- 24% worried about side effects
How do you know it’s safe?

Institute of Medicine: August 2011
IOM Immunization Safety Review

- MMR Vaccine and Autism
- Thimerosal-Containing Vaccines and Neurodevelopmental Disorders
- Multiple Immunization and Immune Dysfunction
- Hepatitis B Vaccine and Demyelinating Neurological Disorders
- Simian Virus-40 Contamination of Polio Vaccine and Cancer
- Vaccines and Sudden Unexpected Death in Infancy
- Influenza Vaccine and Neurological Complications
- Vaccines and Autism
US Recommended Schedule for Persons Aged 0-18 Years (2014)

Figure 1. Recommended immunization schedule for persons aged 0 through 18 years – United States, 2014. (For those who fall behind or start late, see the catch-up schedule [Figure 2].) These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are in bold.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>19-23 mos</th>
<th>2-3 yrs</th>
<th>4-6 yrs</th>
<th>7-10 yrs</th>
<th>11-12 yrs</th>
<th>13-15 yrs</th>
<th>16-18 yrs</th>
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<tbody>
<tr>
<td>Hepatitis B (HepB)</td>
<td>1st</td>
<td>2nd</td>
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<td>3rd</td>
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<td>Rotavirus* (RV) RV1 (2-dose series)</td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
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<td>Diphtheria, tetanus, &amp; acellular pertussis</td>
<td>1st</td>
<td>2nd</td>
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<td>5th</td>
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<tr>
<td>Tetanus, diphtheria, &amp; acellular pertussis</td>
<td>1st</td>
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<td>3rd</td>
<td>4th</td>
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<td>5th</td>
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<td>Haemophilus influenza type b (Hib)</td>
<td>1st</td>
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<td>Pneumococcal conjugate* (PCV13)</td>
<td>1st</td>
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<td>Pneumococcal polysaccharide* (PPSV23)</td>
<td>1st</td>
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<td>Inactivated poliovirus* (IPV) (&lt;18 yrs)</td>
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<td>2nd</td>
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<td>Influenza* (IV; LAIV)</td>
<td>1st</td>
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<td>Measles, mumps, rubella* (MMR)</td>
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<td>Varicella* (VAR)</td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
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<tr>
<td>Hepatitis A* (HepA)</td>
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<td>2nd</td>
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<tr>
<td>Human papillomavirus* (HPV2: females only; HPV4: males and females)</td>
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<td></td>
<td>2nd</td>
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<tr>
<td>Meningococcal* (Hib-MenCY d; MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos)</td>
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<td>2nd</td>
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**Range of recommended ages for all children**

**Range of recommended ages for catch-up immunization**

**Range of recommended ages for certain high-risk groups**

**Range of recommended ages during which catch-up is encouraged and for certain high-risk groups**

This schedule includes recommendations as of January 1, 2014. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at [http://www.cdc.gov/vaccines/hcp/acip-recs/index.html](http://www.cdc.gov/vaccines/hcp/acip-recs/index.html). Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online ([http://www.vaers.hhs.gov](http://www.vaers.hhs.gov)) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautionary and contraindications for vaccination, is available from CDC online ([http://www.cdc.gov/vaccines/recs/vac-advm/contraindactions.htm](http://www.cdc.gov/vaccines/recs/vac-advm/contraindactions.htm)) or by telephone (800-CDC-INFO (800-232-4636)).

This schedule is approved by the Advisory Committee on Immunization Practices ([http://www.cdc.gov/vaccines/acip](http://www.cdc.gov/vaccines/acip)), the American Academy of Pediatrics ([http://www.aap.org](http://www.aap.org)), the American Academy of Family Physicians ([http://www.aafp.org](http://www.aafp.org)), and the American College of Obstetricians and Gynecologists ([http://www.acog.org](http://www.acog.org)).

**NOTE:** The above recommendations must be read along with the footnotes of this schedule.
Addressing Parents’ Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant’s Immune System?

Paul A. Offit, MD†; Jessica Quarles‡; Michael A. Gerber, MD§; Charles J. Hackett, PhD∥; Edgar K. Marcuse, MD∥; Tobias R. Kollman, MD∥; Bruce G. Gellin, MD**; and Sarah Landry‡.

ABSTRACT. Recent surveys found that an increasing number of parents are concerned that infants receive too many vaccines. Implicit in this concern is that the infant’s immune system is inadequately developed to handle vaccines safely or that multiple vaccines may overwhelm the immune system. In this review, we will examine the following: 1) the ontogeny of the active immune response and the ability of neonates and young infants to respond to vaccines; 2) the theoretic capacity of an infant’s immune system; 3) data that demonstrate that mild or moderate illness does not interfere with an infant's ability to generate protective immune responses to vaccines; 4) how infants respond to vaccines given in combination compared with the same vaccines given separately; 5) data showing that vaccinated children are not more likely many as 20 shots by 2 years of age (Table 1). The increased number of vaccines given to children and the increased percentage of children receiving vaccines have resulted in a dramatic decrease in the number of vaccine-preventable diseases. Most young parents today have never seen many of the diseases that vaccines prevent. As a possible consequence of these trends, recent national surveys found that 23% of parents questioned the number of shots recommended for their children, and 25% were concerned that vaccines might weaken the immune system.

Because most parents receive information and recommendations about vaccines from their doctors, and because these recommendations carry substan-
While the number of vaccines has increased, the antigen content of infant vaccines has decreased.
WHO Director-General Expresses Concern Over Public Mistrust Of Vaccines

“During the WHO’s Executive Board meeting, WHO Director-General Margaret Chan expressed concerns over what she called a "'worrisome' public mistrust of vaccines..."

Agence France Press: January 18, 2011
We have all been in denial at some point in our lives; faced with truths too painful to accept, rejection often seems the only way to cope.

Under those circumstances, facts, no matter how detailed or irrefutable, rarely make a difference. Denialism is denial writ large – when an entire segment of society, often struggling with the trauma of change, turns away from reality in favor of a more comfortable lie.
Autism and Vaccines

Did the recent news that a study linking autism to vaccines had been called a fraud by medical researchers affect your opinion about vaccines?

- Yes, I now believe there is a link: 5.6%
- No, I never believed the link: 53.9%
- Yes, I no longer believe in the link: 12.6%
- No, I still believe in the link: 27.9%

Source: WebMD online survey of 764 U.S. parents, Feb. 22-March 7, 2011; +/- 3.5% margin of error
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Everyone is entitled to their own opinions...but no one is entitled to their own facts.

Daniel Patrick Moynihan
“Then we’ve agreed that all of the evidence isn’t in, and that even if all of the evidence were in, it still wouldn’t be definitive”