The Value of Vaccines

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Variolation Pre-dates Vaccination

- History of “Vaccination” begins with “Variolation” i.e. the intentional inoculation with “Smallpox” or “Variola” to prevent the disease.
- Some scholars say that “Variolation” might have originated in India and attributed to Dhanvantari, founder of the Vedic Tradition in ~ 1500 BC.
- Others say it was first used in Chinese Medicine during the 10th Century AD.
Introduction of Variolation to the West

- The practice was introduced to the west by Lady Mary Wortley Montagu (1689 – 1762).
- Lady Montagu's husband, Edward Wortley Montagu, served as the British ambassador to the Ottoman Empire from 1716 to 1717.
- She witnessed inoculation being practiced by physicians in Istanbul, and was greatly impressed.
- She had her children inoculated by variolation.
- The practice slowly gained popularity in the West.
Edward Jenner – Dawn of the Vaccine Era

1749 - 1823
Jenner’s House – Birthplace of “Vaccination”
An 18th century small building of stone under a thatched roof. It is decorated around its doorway and inside with large sections of bark from forest trees. It contains a small fireplace. In this building Edward Jenner vaccinated the poor people of the district, without charging any fees.
Sarah Nelmes – The Milkmaid who Helped to give Birth to “Vaccination”

The hand and upper arm of Sarah Nelmes (1798). Photo courtesy of the National Library of Medicine
Edward Jenner Vaccinating James Phipps

1796
1802 caricature of Jenner vaccinating patients who feared it would make them sprout cow-like appendages.
The medical establishment, as cautious then as now, considered his findings for some time before accepting them. Eventually vaccination was accepted, and in 1840 the British government banned variolation – the use of smallpox itself – and provided vaccination – using cowpox – free of charge.
The word “vaccination” was first used by Edward Jenner in 1796.

Vaccination (Latin: *vacca* - cow) is so named because the first vaccine was derived from the relatively benign cowpox virus, which provides a degree of immunity to smallpox, a contagious and deadly disease.

In common speech, “vaccination” and “immunization” in general have the same colloquial meaning.
Louis Pasteur and the World’s First Rabies Vaccine

1822 – 1895

He developed his rabies vaccine by growing the virus in rabbits, then drying the affected nerve tissue to weaken the virus. On July, 1885, the vaccine was administered to Joseph Meister, a 9-year-old boy who had been attacked by a rabid dog. The boy survived and avoided contracting rabies, which would have almost certainly proved fatal.
Joseph Meister and Pasteur’s Rabies Vaccine

1876 - 1940
Vaccination Strategies

**Prophylactic Vaccine:** Administered before exposure to an infectious agent (or soon after exposure in certain cases).

⇒ **Prevention**

**Therapeutic Vaccine:** Administered during an active infection.

⇒ **Treatment**
Traditional Vaccines

- **Types:**
  - Inactivated (Killed): DPT
  - Live-attenuated: MMR, BCG

- **Using whole Microbes:**
  - Virus
  - Bacteria
  - Parasites
Major Vaccine Types

Protein Subunit Vaccines:
- Hepatitis B Vaccine (HBsAg)
- Human Papillomavirus (HPV) Vaccine (L1)
- Influenza Vaccine (H and N)

Conjugate Vaccines:
- *Haemophilus influenzae* type B Vaccine.
- Pneumococcal Conjugate Vaccine.

Combination Vaccines:
- **Bivalent:** OPV (Type 1 + Type 3)
- **Trivalent:** DPT, MMR
- **Tetravalent:** DPT + IPV
- **Pentavalent:** DPT + HepB + Hib
- **Hexavalent:** DPT + HepB + Hib + IPV
Adjuvants

- Enhance immunogenicity.
- Reduce amount of antigen.
- Reduce number of immunizations.

Human Use

Aluminium Salts
- Aluminium phosphate sulphate or Alum
- Aluminium hydroxide
- Aluminium phosphate

Oil Emulsions
- MF59™ - Uses Squalene (Chiron, now Novartis).
- QS-21 – Purified saponin from the bark of *Quillaja saponaria*.
- MPL™ - Monophosphoryl Lipid A from *Salmonella minnesota* (Corixa).
- ASO4 – Aluminium salt + MPL (GSK).

Animal Use
- Complete Freund’s Adjuvant (CFA)
- Incomplete Freund’s Adjuvant (IFA)
Vaccination as a Disease Prevention Tool
Vaccination for Preventing Diseases

- Vaccination, as a preventive strategy, is considered to be the most cost-effective medical intervention in the fight against infectious diseases.

- **Vaccination Success Story:** Diseases that are under control / nearly eliminated in developed countries – MMR, Hepatitis B, Hib and DPT. Polio nearly eradicated.

- With the exception of clean, safe drinking water, proper sanitation, and housing, no other medical intervention rivals vaccination in tackling infectious diseases and reducing mortality rates.
Vaccines: Facts and Figures

- Currently, **vaccines** are available against **26 infectious diseases** – many more in the pipeline.
- **Before smallpox eradication** in 1977, the disease threatened **60% of the world’s population**.
- Between 1999 and 2003, **measles deaths decreased** worldwide by almost **40%**.
- **Vaccines save over 2 million children** every year.
Vaccination can prevent major childhood diseases.
Child Mortality in India

- Pneumonia: 20%
- Diarrhea: 13%
- Measles: 4%
- Meningitis: 2%
- Pertussis: 5%
- Preterm birth complications: 14%
- Birth asphyxia: 10%
- Neonatal sepsis: 7%
- Congenital abnormalities: 3%
- Other: 22%

Year of estimate: 2008

Causes of Death for 2 Million Children Under Age 5, by State Group, 2004

EAGA: Empowered Action Group states plus Assam

SOURCE: Jha and Laxminarayan (2009) Choosing Health - An Entitlement for all Indians, CGHR
Pneumonia – Major Etiologic Agents

Streptococcus pneumoniae
- Gram Positive Bacterium

Haemophilus influenzae Type B
- Gram Negative Bacterium
Major Symptoms of Pneumococcal and Hib Infections
Pneumococcal Vaccines

**Prevnar**

- **7-valent vaccine**, manufactured by Wyeth. In the USA, vaccination with Prevnar is recommended for all children <2 years, and for unvaccinated children (24-59 months) at high risk for pneumococcal infections.
- Replaced with the new **Prevnar-13** (Pfizer), approved by US-FDA in February 2010. **Price: 5,800 INR**

**Synflorix**

- **10-valent vaccine**, produced by GSK. Contains 10 serotypes of pneumococcus conjugated to a carrier protein.
- GSK received European Commission authorization to market Synflorix in March 2009.
Hib Vaccines

- First Hib vaccine licensed was a pure polysaccharide vaccine, first marketed in the US in 1985.

- **Conjugate Vaccine:** The shortcomings of the polysaccharide vaccine led to the production of the Hib polysaccharide-protein conjugate vaccine. Attaching Hib polysaccharide to a protein carrier greatly increased the ability of the immune system of young children to recognize the polysaccharide and develop immunity.

- Hib conjugate vaccines have been effective against all manifestations of Hib disease, with a clinical efficacy between 95-100%.
## Indian Hib Combo Vaccines

<table>
<thead>
<tr>
<th>Company</th>
<th>Type of Vaccine</th>
<th>Date of WHO Pre-qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Institute of India Ltd.</td>
<td>Quadrivalent: DPT (whole cell) + Hib</td>
<td>June 23, 2010</td>
</tr>
<tr>
<td>Serum Institute of India Ltd.</td>
<td>Pentavalent: DPT (whole cell) + HepB + Hib</td>
<td>May 26, 2010</td>
</tr>
<tr>
<td>Biological E Ltd.</td>
<td>Pentavalent: DPT (whole cell) + Hep B + Hib</td>
<td>August 31, 2011</td>
</tr>
</tbody>
</table>
Diarrhoeal Disease in Children
Diarrhoea – A Major Killer of Children!

- **4.6 million children below 5 years of age die of diarrhoeal diseases** ⇒ This constitutes **19%** all childhood deaths.
- **85% of diarrhoeal deaths occur in the first year of life.**
- **In India, 0.3 million deaths occur annually in children below 5 years of age**


Aetiological Agents

- **Virus**
  - Rotavirus*
  - Norovirus*

- **Bacteria**
  - Enterotoxigenic E. coli
  - Shigella*
  - Salmonella
  - Vibrio Cholerae*
  - Campylobacter jejuni
  - Yersinia pestis

- **Protozoan Parasites**
  - Giardia
  - Entamoeba histolytica
  - Cryptosporidium

* Common Causes of epidemic diarrhoea

Rotavirus Diarrhoea
Rotavirus

- Leading cause of diarrhoea in infants and young children worldwide.
- Causes >0.5 million deaths in children <5 years of age.

Rotavirus Gastroenteritis

Classical symptoms in all age groups include fever and vomiting for 2-3 days ⇒ Non-bloody diarrhoea

Source: http://www.cdc.gov/rotavirus/index.html
Rotavirus (RV) Type A: The Most Common Cause of Infections in Humans

Globally: Rotavirus causes 40% of all diarrhoea and 527,000 deaths annually in infants.

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>23.2%</td>
<td>122,270</td>
</tr>
<tr>
<td>Nigeria</td>
<td>9.5%</td>
<td>49,974</td>
</tr>
<tr>
<td>DR Congo</td>
<td>5.8%</td>
<td>30,444</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>5.2%</td>
<td>27,424</td>
</tr>
<tr>
<td>China</td>
<td>5.2%</td>
<td>27,349</td>
</tr>
<tr>
<td>Pakistan</td>
<td>3.8%</td>
<td>19,933</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>3.4%</td>
<td>17,992</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>2.9%</td>
<td>15,382</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2.5%</td>
<td>12,970</td>
</tr>
<tr>
<td>Angola</td>
<td>2.1%</td>
<td>11,229</td>
</tr>
<tr>
<td>Niger</td>
<td>2.1%</td>
<td>10,884</td>
</tr>
</tbody>
</table>

20-30% of hospitalized patients with diarrhoea +ive for rotavirus.
Rotavirus Vaccines
Licensed Oral Rotavirus Vaccines (ORV)

• **Rotarix™ (GSK, Belgium)** – Human monovalent live attenuated RV strain (RV1). Intl. License. **Price: 5,255 INR**

• **RotaTeq™ (Merck, USA)** – Pentavalent live bovine-human reassortant RV strain (RV5). Intl. License. **Price: 3,536 INR**
Rotavirus Vaccines: The Problem of Low Vaccine Efficacy in Developing Countries

Rotarix™ Trials in South Africa and Malawi

Randomized, Placebo-controlled, Multicenter Trial

Vaccine Efficacy

- South Africa: 76.9%
- Malawi: 49.4%

Efficacy far lower in Malawi!

NEJM 2010; 362: 289-98.
The Indian ORV 116E Holds Promise for Developing Countries

- $1 \times 10^5$ Focus forming unit found safe and immunogenic in clinical trials in USA and India. Robust immune response after 3 administrations.
- 4 fold increase rotavirus IgA titer in 89.7% of infants recipient of ORV.
- Technical Collaborators: DBT (India), CDC (USA), NIH (USA), Stanford University and PATH
- Development by Bharat Biotech International Limited (Hyderabad, India)


Neonatal strain 116E Isolated at AIIMS New Delhi
Other Indian Rotavirus Vaccines in the Pipeline

- **Bharat Biotech Limited**: Has plans to develop a Rotavirus vaccine “Rotavac”, priced at only USD1 in collaboration with GAVI and DBT.

- **Sanofi Pasteur (Shantha Biotech)**: In collaboration with PATH, coming up with Rotavirus vaccines.
Tackling Childhood Diarrhoea – Other Strategies

Direct:
- Oral Rehydration Therapy.
- Zinc Supplementation.

Indirect:
- Improvements in Hygiene and Sanitation.

Source: http://www.who.int/immunization/topics/rotavirus/en/
Other Important Vaccine Trials for Enteric Diseases
Cholera Vaccine Trials, Kolkata

NICED – IVI / DOMI Collaborative Projects

Safety and immunogenicity (Phase-II) and RCT (Phase-III) trials of bivalent (01 and 0139) killed, whole cell oral cholera vaccine in Indian subjects in Kolkata, West Bengal

Developed by IVI and ICMR with funding from BMG Foundation. Technology transferred to Shantha Biotech for commercial development. Now marketed as Shanchol™

In April 2009 policymakers in India decided in a meeting (pictured) organized by the IVI and India's National Institute of Cholera and Enteric Diseases (NICED) to conduct a pilot cholera vaccination program in a highly cholera-endemic rural area of Orissa, using the Shanchol™ vaccine.
Typhoid Vaccine Trials, Kolkata

NICED – IVI / DOMI Collaborative Projects

- Randomized controlled evaluation of protection by the Vi polysaccharide vaccine against typhoid fever in Kolkata, West Bengal
  - To determine the protective effectiveness of the Vi polysaccharide vaccine
  - To monitor the safety and immunogenicity of the Vi polysaccharide vaccine

**Typherix® (Trial Vaccine)**
25 ug Vi polysaccharide of *S. typhi* (adults and children)
Licensed in India

**Havrix® (Placebo)**
1440 EL.U. of viral antigen – Adults
720 EL.U. of viral antigen – Pediatrics
Licensed in India

**Major Findings**
- *Vi vaccine conferred 61% protection*
- *Highly protective in young children (80%)*
- *Showed indirect protection (44%) in non-vaccinated neighbors of Vi-vaccinees*
- *Overall protection - 57%*
- *Evidence shows that this vaccine may be introduced in typhoid endemic zone*
Other Major Vaccine Trials in India
HIV / AIDS Vaccine Candidates: Phase - I Clinical Trials

tg AACO9 HIV-1 Vaccine Phase 1 Trial, NARI, Pune:
- Vaccine well tolerated at 3 doses used.
- Weakly immunogenic.
- Evidence of high baseline titer of AAV2 neutralizing antibody in Indian population as compared to European participants.

MVA Vaccine Trial, TRC, Chennai:
- Dose-dependant response seen.
- TBC-M4 immunogenic at both low and high dose with 75% and 100% of low and high dose vaccinees responding after 3 injections.
- Most responses were balanced, directed to both env and gag, then against pol, nef or tat-rev.
- Lack of impact of previous smallpox vaccination on response rate.

TBC-M4 (Modified Vaccinia Ankara (MVA) HIV-1 multigenic subtype C) Vaccine
Measles Aerosol Vaccine Trial

- National Institute of Virology - KEM, Pune
- NICED - BC Roy Children Hospital, Kolkata
- National Institute of Epidemiology - King Institute - Institute of Child Health, Chennai
- Study funded by WHO
India is a Supplier of World-Class Vaccines
India has a Strong Presence in the Global Vaccine Scenario

- Majority of Indian Vaccine Suppliers are WHO Prequalified.
- Developing Country Vaccine Manufacturers Network (DCVMN) – Indian Members:
  - Bharat Immunologicals & Biologicals Corp.
  - Indian Immunologicals Ltd.
  - Bharat Biotech Intl. Ltd.
  - Haffkine Bio-Pharmaceutical Corp. Ltd.
  - Panacea Biotec
  - Biological E
  - Serum Institute of India
  - Zydus Cadila
  - Chiron Behring Vaccines Pvt. Ltd.
## Major Players in the Indian Vaccine Industry

<table>
<thead>
<tr>
<th>Company</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shantha Biotech, Hyderabad</td>
<td>Hepatitis B (recombinant), DTwP-Hep B (Shantetra), TT (Shan TT), DTwP-Hepatitis B-Hib (Shan5) (1 dose and 10 doses)</td>
</tr>
<tr>
<td>Panacea Biotec, New Delhi</td>
<td>DTwP Biofarma - Hib Novartis (EASYFOUR), DTwP Biofarma - Hepatitis B PHB (ECOVAC), DTwP Biofarma - Hep B PHB- Hib PHB (EASYFIVE), Hepatitis B (Enivac B), OPV (from bulk supplied by Biofarma, Indonesia), OPV (from bulk supplied from Chiron, Italy)</td>
</tr>
<tr>
<td>Zydus Cadila, Ahmedabad</td>
<td>Rabies, Influenza</td>
</tr>
<tr>
<td>Serum Institute of India, Pune</td>
<td>BCG, DT, dT, DTwP, DTwP-Hep B, Hep B (recombinant), TT, MR, MMR, measles, rubella</td>
</tr>
<tr>
<td>Haffkine, Mumbai</td>
<td>OPV (from bulk supplied by Biofarma, Indonesia)</td>
</tr>
</tbody>
</table>
Vaccines: Major Contributions by Indian Companies
Shantha’s Contributions: Recombinant Hepatitis B and Cholera Vaccines

Shanchol: Developed by IVI and ICMR with funding from BMG Foundation. Technology transferred to Shantha Biotech for commercial development.
Serum Institute of India’s Meningococcal A Conjugate Vaccine – A Boon for Africa

MenAfriVac (Meningococcal A Conjugate vaccine) is a lyophilized vaccine of purified meningococcal A polysaccharide covalently bound to tetanus toxoid (TT), which acts as a carrier protein. The vaccine consists of purified group-specific bacterial polysaccharide from *Neisseria meningitidis* group A.

Meningitis Vaccine Project

- **2010-2012**: 55 million people vaccinated, aged 1-29 years.
- **2011**: 21 million people vaccinated in Cameroon, Chad and Nigeria.
Vaccine Clinical Trial Facilities

- National Institute of Cholera and Enteric Diseases (NICED), Kolkata
- National Institute for Research in Tuberculosis (NIRT)*, Chennai
- Vadu Rural Health Program, King Edward Medical (KEM) College and Hospital, Mumbai
- Postgraduate Institute of Medical Education and Research (PGI), Chandigarh
- Christian Medical College (CMC), Vellore
- National AIDS Research Institute (NARI), Pune
- Society for Applied Studies (SAS), Kolkata and New Delhi
- Medanta Duke Research Institute (MDRI) – A Joint venture partnership between Duke Medicine and Medanta Medicity in New Delhi – Early phase clinical site (up-coming)
- Quintiles & Apollo – Clinical Trials Unit at Hyderabad (up-coming)

* Formerly Tuberculosis Research Centre (TRC)
State-of-the-Art Vaccine Trial Facilities, NARI

Information / Education Room

Clinical Room

Immunology Lab
State-of-the-Art Vaccine Trial Facilities, NIRT *

* Formerly Tuberculosis Research Centre (TRC)
New Vaccine Technologies
DNA Vaccines
DNA Vaccine Construct

- Multiple Cloning Site – For inserting the gene of interest.
How do DNA vaccines work?
DNA Vaccine: Delivery
The Helios® Gene Gun
Gene Gun: Principle of Operation

- **Gold Microparticles**: 1 µm diameter
- **Helium Gas**
- **Firing Pressure**:
  - Mice: 200 psi
  - Monkey: 500 psi
Advantages of DNA Vaccines

- **Safer to produce**, since culture of dangerous infectious agents are not involved.
- Since only DNA is used, there is no chance of virulence due to reversion.
- **Cheaper to produce**, since protein expression and purification is not involved.
- **Logistically feasible**, since cold-chain will not be required due to stability of DNA.
- **Economically feasible**, since one plasmid can encode for more than one antigen.
Fears about DNA Vaccines

- DNA integration.
- Autoimmunity.
- Immunologic tolerance.

No supporting data so far...
Virus Like Particles – A Novel Vaccine Platform
Virus Like Particles

- **Virus-like particles (VLPs)** resemble viruses, but are **non-infectious** because they do not contain any viral genetic material.

- The expression of viral **structural proteins**, such as Envelope or Capsid, can result in the **self-assembly** of VLPs.

- **VLP Technology** has been employed for vaccine development against a variety of viruses, including **Influenza Virus** and **Human Papilloma Virus (HPV)**.
Expression Systems

Prokaryotic (Bacteria)

- E. coli

Eukaryotic (Yeast)

- Saccharomyces cerevisiae
- Pichia pastoris
- Hansenula polymorpha
72 Pentamers (Capsomeres) of L1 Comprise the Viral Capsid
Atomic Structure of HPV16 L1 Pentameric Capsomeres
VLPs Structurally Resemble the Viral Capsid
*In vitro* assembly may generate particles of different sizes.
Capsomerses Spontaneously Assemble \textit{in vitro}

TEM of VLPs
VLP based Vaccines being Developed in India

DBT, Government of India

- HPV Vaccine ⇒ R&D

Cadila Biopharmaceuticals

- Joint Venture between Cadila and Novavax (USA)
  ⇒ H1N1 Vaccine (R&D and Scale-up)
Infectious Diseases for which Vaccines are Urgently Needed – The BIG THREE!
Tuberculosis

- No vaccine except BCG.
- **AERAS Vaccine Candidates**: MVA85A, AERAS-402, GSK M72, AREAS-422 (rBCG), SSI / SP H4-IC31

Malaria

- Recombinant fusion protein of *P. falciparum* CSF + HBsAg: Initial Phase III Trials completed. Final Phase III data will be available in 2014.
- Other candidates, many years behind.

HIV/AIDS

- No vaccine successful yet.
- RV144 Trial completed in Thailand.
- **Ongoing Trials**: UKHVC, BMGF, CHAVI-ID
Elucidating the Value of Vaccines
Socio-Economic Value of Vaccination

• An important tool for increasing attendance:
  • In schools and colleges.
  • In offices.

• An important tool for poverty reduction:
  • Potential to reduce burden of major diseases of poverty, with availability of new vaccines e.g. TB, Rheumatic Fever / Rheumatic Heart Disease, etc.
  • Potential to reduce Neglected Tropical Diseases (NTDs) like Kala-azar, with availability of new vaccine e.g. LEISHHDNAVAX.
Vaccination Efforts Need to be Sustained in Order to be Effective

- Sustained vaccination efforts have eradicated smallpox and lowered the global incidence of polio by 99%.

- Historical evidence indicates that decrease in vaccination efforts leads to reappearance of disease.

- Vaccination has averted 7.5 million deaths from measles.
Vaccination – Problems Remain

- In all, 3 million people die each year from vaccine preventable diseases – (Center for Global Development, 2005)
- Declining funding for immunization has been mirrored in stagnating or falling coverage.
- Global coverage of the DPT vaccine has been stalled at around 74% since 1990 – (GAVI, 2003)
- 57 developing countries have yet to eliminate neonatal tetanus, and 200,000 babies died of the disease in 2000 – (WHO, 2002)
Loss in Momentum in Universal Vaccine Coverage – Why?

- Easiest-to-reach populations have already been vaccinated. Unvaccinated populations living in inaccessible areas.

- Practical problems impeding vaccine delivery:
  - Lack of good roads and reliable transportation.
  - Lack of knowledge of the value of vaccines, hence reluctant to be vaccinated.
  - Lack of trained staff and accessories (sterile syringes).
  - Lack of constant power supply.

- Political Reasons: Immunization campaigns cannot operate in isolation; they are dependent on the prevailing political and social environment.

- Economic Reasons: Vaccines like PCV and HPV currently too expensive.
Disparities in Immunization Rates

Vaccine Development –
A Long and Arduous Process

- The process of researching, testing, gaining regulatory approval and manufacturing vaccines is a costly, complex and lengthy process.

- Developing a new vaccine takes on average 18.5 years and costs over USD 800 million.

- Such sustainable investment requires long-term commitment, predictable future demand and government policies that recognize the value of vaccination.

- Long-term partnership and collaboration between policy makers, public health authorities and industry is also crucial.
Vaccine Development: A Costly Affair!

- Laboratory Development
  - Technology Transfer
    - GMP Grade Material
      - Preclinical Toxicity
        - Phase I trial
          - No Go
        - Phase II trial
          - No Go
        - Phase III trial
          - No Go
      - Production
        - No Go
  - Post-marketing surveillance further adds to the cost!
The technological revolutions of the last 25 years shortened the path of discovery of new vaccines. However, while the discovery phase of vaccines is much shorter, today the development path, which costs approximately 10-fold than discovery, is much longer than in the past. (a) Vaccine discovery and development path in 1980; (b) vaccine discovery and development path in 2000.

Source: Vaccine 2003; 21: S2/110
Historical Attractiveness of Vaccine Investment

Source: Science 2002; 297: 937
Social vs Economic Value of Vaccines

Source: Science 2002; 297: 937
What’s the Value of a Vaccine if it’s Under-utilized?

Examples:

- **Hepatitis B Vaccine** ⇒ Programmatic Issue.
- **HPV Vaccine** ⇒ Too Expensive.
- **Cholera Vaccine (Shanchol)** ⇒ Lack of political commitment.
Intangible Value of Vaccination

Infectious Diseases can wipe-out entire cities ...
The original front of the Siena cathedral, as it is nowadays. The front wall of the cathedral of Siena, the construction of which was interrupted by the plague in 1348. The plague wiped out over 70% of the population. The wall, with its gaping, monumental, windows, stands 664 years after the plague as a reminder of how devastating infectious diseases can be and represents the largest “monument to infectious disease” ever built by mankind.
Thank You!