Challenges of Evidence-based Decision in Developing countries

Lessons from the recent Hib vaccine experience

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ADVAC, May 2010
Vaccine Development and implementation: a continuum
“Evidence-based” or “Evidence-informed” Decision Making

a decision process that is based on an unbiased assessment of the available information

• Decision process: a conscious process (as opposed to inaction/avoidance) that results in a decision (yes/no/wait)

• Unbiased: preconceptions and biases are addressed so that the decision can be primarily based on evidence

• How much data is needed? Use available evidence: Additional information is not always required. However, an evidence-based decision could be to collect additional information.
Historically 15-20 years passed before new vaccines reached poorest children.
Why does it take so long for vaccines to be introduced in developing countries?

- Vaccine “value” factors:
  - Disease burden
  - Vaccine efficacy/impact
  - Vaccine cost-effectiveness
  - Vaccine safety

- Health systems factors:
  - Existence/ strength of process (immunization advisory committee a key factor)
  - Vaccine cost and financing, supply
  - Program considerations: Coverage, Cold Chain, trained personnel ....
  - Planning

- Policy factors: what generates “political will”?
  - Global: Strong and clear recommendations, donor commitment
  - Competing priorities/ focus on broader context (e.g. child survival)
  - Global and local stakeholders
  - Decision making context: a “policy” window
  - Political considerations

Awareness of the significance of these factors and coordination are very important but often overlooked.
Steps for Decision Making

- Policy decision
- Programme issues
- Financing
- Priority
- Cost-effectiveness
- Vaccine
- Burden
Factors affecting evidence-based decisions

Vaccine value

Evidence-based decisions

Health systems

Policy context
Why are developing countries not adopting the Hib vaccine?
Hib Disease – A Serious Problem in Children < 5 yrs old

• Meningitis
  – Hib leading cause of bacterial meningitis
  – Mortality up to 30%
  – Long term sequelae: 15 - 35%

• Pneumonia
  – Hib accounts for over 20% of severe pneumonia
  – Mortality: 2-20%

• 3 million children ill/yr, almost 400,000 deaths/yr
Hib Disease is Preventable

• Hib conjugate vaccines:
  – Excellent safety record
  – High efficacy (over 90%)
  – Compatible with EPI schedules
  – Additional advantage: Herd immunity

Routine use has led to virtual elimination of disease in many parts of the world
The Gambia Hib Vaccine Experience

Incidence of Hib Meningitis/100,000 (children <5 years) in the Western Region of the Gambia

Adapted from Adegbola R et al. Lancet, 2005
GAVI-Global Alliance for Vaccines and Immunizations

GAVI is an alliance

Governments - industrialized countries
Governments - developing countries
Non-governmental organizations
WHO
UNICEF
Vaccine industry - industrialized countries
Vaccine industry - developing countries
Research and public health institutes
The Bill & Melinda Gates Foundation
The World Bank Group

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Despite availability of an effective and safe vaccine for over 15 years, and availability of GAVI support for 5 years,

75% of the world’s children still don’t have access to Hib vaccine
The Hib Initiative – A Consortium of Academic and Public Health Institutions

“To expedite and sustain evidence-informed decisions at the global, regional and country levels regarding the use of Hib vaccination to prevent childhood meningitis and pneumonia”
Routine Hib immunization programs 2005

101 countries, including 19 (25%) GAVI countries

GAVI countries:
- Introduced
- No GAVI application made
Assessing the needs

• Country visits
• Formative research
• Regional forums
• Continuous interactions with countries to evaluate changing priorities
• Country consultants
Barriers for Introduction of Hib Vaccine in Developing Countries

• Under-recognition of disease burden
  – Good surveillance data/ systematic studies rarely available
  – Limited data from Asia and Eastern Europe
  – Disease burden difficult to measure accurately
Barriers for Introduction of Hib Vaccine in Developing Countries

• Under-recognition of disease burden

• Financial considerations
  – High cost: $2.50 (monovalent)- $3.65 (DTP-HepB-Hib)
  – Pentavalent vaccine - Single manufacturer—no reduction in price in 4 yrs
  – Concerns about sustainability
Obstacles for Introduction of Hib Vaccine in Developing Countries

• Under-recognition of disease burden

• Financial considerations:

• Lack of awareness, communication and focus:
  – Competing health priorities
  – Disease burden/ vaccine impact often not communicated to or poorly understood by decision makers
  – WHO recommendation “based on burden”, “not strong”
Strategic Approach

- Communication
- Evidence-informed decisions
- Research and Surveillance
- Coordination
What are the pieces of evidence?

- Burden – Mortality, morbidity, cost (local, regional, global)
- Vaccine impact
- Financial considerations: cost of vaccine, cost-effectiveness
- Programmatic considerations: Vaccine supply, safety, logistics (cold chain, feasibility, …)
- Global situation: status of vaccine introduction, recommendations, relationship to MDGs
- Sociopolitical considerations
Vaccine value: disease and vaccine data

Hib Meningitis Studies in Asia
(Children <5 years of age)

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Why does it take so long for vaccines to be introduced in developing countries?

• Vaccine “value” factors:
  – Disease burden, value of surveillance
  – Vaccine efficacy/impact
  – Vaccine cost-effectiveness
  – Vaccine safety

• Health systems factors

• Policy factors
Hib - A difficult organism to study

- Organism factors: Fastidious, sensitive to environment

- Laboratory challenges – lack of adequate infrastructure
  - Lack of good clinical microbiology laboratories, adequate supplies
  - Specimen handling/transport

- Access to health care
  - Antibiotics before presentation
  - Healthcare utilization patterns

- Diagnostic testing:
  - Meningitis: CSF often not obtained
  - Pneumonia: no sensitive tests, multiple pathogens, needs good radiology
Hib Vaccine Trials: X-ray Confirmed Bacterial Pneumonia Vaccine Efficacy (95% CI)

VE: 21% (5-35%)

VE: 31% (-9-57%)

VE: 22% (-7-43%)

VE: 55% (7-78%)

VE: 32% (-2-54%)

VE: -5% (NS)*

* Not significant for x-ray confirmed pneumonia, but significant for clinical pneumonia

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Emerging data from South Asia

Pakistan: various hospital based studies have confirmed Hib as a significant cause of disease

Bangladesh: case control study confirmed Hib as the leading cause of meningitis and a significant cause of pneumonia
Cost effectiveness (CE) of Hib vaccines

- Need for CE data varied by country/region, mainly driven by burden of disease perception

- Few studies have looked at Hib vaccine CE in developing countries

- Where studied, the vaccine has been shown to be cost-effective to cost-saving (Griffiths and Miners. Rev Pharmacoecon Outcomes Res 2009; 9:333-46).

- Benefit shown depends on burden of disease, cost of care

- CE data not always fully understood, or trusted

- Value of vaccine goes beyond C-E: lives saved, reducing disability, improved productivity and other social benefits…….
Cost-effectiveness of Hib vaccine, Kenya, 2004
(Akumu et al. WHO Bull. 2007)

<table>
<thead>
<tr>
<th></th>
<th>Costs/ case averted (US$)</th>
<th>Costs/ death averted</th>
<th>Costs/ DALY averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undiscounted</td>
<td>235</td>
<td>1,050</td>
<td>16</td>
</tr>
<tr>
<td>Discounted (3% per yr)</td>
<td>240</td>
<td>1,073</td>
<td>34</td>
</tr>
</tbody>
</table>
The important role of surveillance studies and the laboratory – before and after vaccine introduction

- Poor surveillance data can hurt decision
- Need to plan ahead to generate local/regional quality data
- Strengthen the laboratory, esp. for VPDs where laboratory confirmation essential (various syndromes, strains, etc…)
- Customize surveillance studies to meet country needs:
  - Population-based surveillance
  - Sentinel surveillance
  - Infrastructure for vaccine effectiveness studies and cost-effectiveness studies
- Empower local researchers to increase data ownership
- Define data needs: local vs regional vs global: WHO Global Disease Burden for Hib and pneumococcal diseases
Health Systems factors
Why does it take so long for vaccines to be introduced in developing countries?

• Vaccine “value” factors

• Health systems factors:
  – Existence/ strength of process (immunization advisory committee a key factor)
  – Vaccine cost and financing, supply
  – Program considerations: Coverage, Cold Chain, trained personnel…..
  – Multi-year plans (cMYP)

• Policy factors:
  – Global: Strong and clear recommendations, donor commitment
  – Competing priorities/ focus on broader context (e.g. child survival)
  – Political will, Countries “readiness” level
  – Decision making context: a “policy” window
  – Political considerations
New challenge

Newer vaccines are more bulky and more costly

[Graph showing vaccine prices and estimated year of licensure]

- Bubble size indicates volume per full course of each vaccine
- Sources: UNICEF Vaccine projection and PAHO Revolving Fund Vaccine Prices, 2009, AMC price for PCV; Volume includes wastage

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Cold chain, supply, and logistics issues

- Improving vaccine coverage critical, esp. with new and expensive vaccine
- Reducing wastage
- Train more personnel
- Optimal vaccine presentation
- Vaccine management systems
- Vaccine supply systems
- Strengthening peripheral levels
## Financing for Hib-containing vaccines

- **GAVI phase II** New and Under-used Vaccine Support guidelines sent to countries 15 November

- **Through 2015**

- **cMYP or updated multi-year plan needed**

### Co-pay Terms

<table>
<thead>
<tr>
<th>Category</th>
<th>Co-pay</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorest ($1000 GNI/capita, LDC)</td>
<td>$0.23</td>
<td>Gradually increasing co-payment through 2010</td>
</tr>
<tr>
<td>Intermediate ($1000 GNI/capita, not LDC)</td>
<td>$0.38</td>
<td>Fixed co-payment through 2010</td>
</tr>
<tr>
<td>Least Poor (&gt;1000 GNI/capita)</td>
<td>$0.43</td>
<td>Fixed co-payment through 2010</td>
</tr>
<tr>
<td>Fragile States</td>
<td>$0.15</td>
<td>Fixed co-pay, flexible financing through 2010</td>
</tr>
</tbody>
</table>
Pentavalent DTP-HepB/Hib Product Timeline* Summary

- **WHO Pre-Qualified Approval**
- **NRA Licensure Not Pre-Qualified**

### Liquid
- 10 liquid products could be pre-qualified by 2015

### Liquid/lyo
- 6** liquid/lyo products could be pre-qualified by 2012

**The two currently licensed liquid/lyo products are from 1 supplier**
Affordable supply is achievable as new suppliers meet increased demand – Importance of demand and supply forecast

1. As demand in developing countries increases and demand becomes more certain, manufacturers will invest in capacity

2. Increased supply and competition should lead to reduced prices

3. Lower prices encourage increased demand in developing countries.
Importance of assessing impact on programs: Post implementation evaluations (PIE)

- Vaccines are introduced in countries with relatively weak programs (>50% DTP3); WHO recommends evaluation

- Ideally conducted within 6-12 mos of introduction: enough time for program scale up, early enough to correct major problems

- Key findings:
  - Smooth transition from DTP to Pentavalent
  - Good vaccine/disease knowledge among HCWs, & acceptance
  - AEFI system in place
  - Need more support and training at peripheral levels
Developing the infrastructure for a decision making process

- National leadership and ownership
- Functional immunization advisory committees
- Comprehensive annual planning and review
Policy factors
Why does it take so long for vaccines to be introduced in developing countries?

• Vaccine “value” factors

• Health systems factors

• Policy factors: what generates “political will”?
  – Global: Strong and clear recommendations, donor commitment
  – Competing priorities/ focus on broader context (e.g. child survival)
  – Global and local stakeholders
  – Decision making context: a “policy” window
  – Political considerations
Policy context factors that led to accelerated Hib vaccine uptake in GAVI-eligible countries

• Revised WHO Recommendation (Nov. 2006):
  – Global use of Hib vaccine, even when local data not available

• GAVI co-financing guidelines
  – To promote long term sustainability

• Countries need to meet MDG4 (child survival goal)
Vaccines need to be put in context of country priorities: Hib vaccine as a part of a package of interventions to reach MDG4 (*reduce child mortality by 66% by 2015*)

<table>
<thead>
<tr>
<th>Prevention Intervention</th>
<th>Number (thousands)</th>
<th>Deaths prevented as proportion of all child deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastfeeding</td>
<td>1301</td>
<td>13%</td>
</tr>
<tr>
<td>Complementary feeding</td>
<td>587</td>
<td>6%</td>
</tr>
<tr>
<td>Antibiotics for pneumonia</td>
<td>577</td>
<td>6%</td>
</tr>
<tr>
<td>Zinc</td>
<td>459</td>
<td>5%</td>
</tr>
<tr>
<td>Hib vaccine</td>
<td>403</td>
<td>4%</td>
</tr>
</tbody>
</table>
Coordination efforts for Hib vaccine introduction

- Working closely with countries and major partners
- Training activities for programmatic support
- Assessing vaccine demand and supply forecast
Importance of political situation
Need for separate strategies for large countries: India as a case Study
Combating Hib Pneumonia and Meningitis in Tanzania

Childhood Pneumonia and Meningitis

- Pneumonia is the leading infectious cause of death for children globally (WHO, 2005).
- WHO researchers estimate that about 21% of deaths of children under five in Tanzania are due to pneumonia (Figure 2).
- In total, 37,000 Tanzanian children will die of pneumonia each year (WHO/UNICEF, 2006).
- Hib has been shown to cause approximately 20% of severe pneumonia worldwide (Mulholland, 1997).

African countries in which Hib vaccine is not included in routine infant immunization have some of the highest rates of meningitis and pneumonia in the world. Due to these high rates of disease and the resulting mortality, WHO and the African Task Force on Immunization (TFI) currently recommend that all countries adopt Hib vaccine, emphasizing that lack of local data should not be a cause for delay. As of May 2007, 15 countries have introduced Hib vaccine, and a significant number have adopted Hib vaccine programs. As a result, there has been a substantial reduction in morbidity and mortality from Hib-related disease in those countries where Hib vaccine has been introduced. If Tanzania was to adopt Hib vaccine into its routine immunization program an estimated 8,262 deaths could be prevented annually (Figure 1).

Although data on pneumonia and meningitis in Tanzania remain limited, data from surrounding countries suggest that disease burden is high. Data have also shown that Hib is the primary cause of bacterial meningitis and a significant cause of particularly lethal forms of pneumonia.

Figure 1: Estimated* number of annual childhood deaths averted through Hib vaccination

*Estimates derived from 4% expected reduction in under five mortality from Hib vaccination (Jones, 2003). Based on 2005 number of live births and vaccination coverage.

Figure 2: Cause of death in Tanzanian children less than 5 years of age

- Neonatal: 27%
- HIV/AIDS: 9%
- Measles: 1%
- Malaria: 23%
- Pneumonia: 21%
- Injuries: 2%
- Other: 0%
- Diarrheal Diseases: 17%


Communications

- GOAL: Raise awareness of Hib and increase sense of urgency for decision making
- Partnered with pediatric associations, civil society, country experts, WHO, country MOHs, to deliver messages
- Information tailored for region and country level
Empowering Countries for Decision Making - Providing Evidence & Tools

- Surveillance and research to estimate burden (GDB) and document impact (RFP)
- Briefing packets
- Financing guidelines
- Supply analysis
- CE analysis tool
- Helping to develop decision process

In Asia, studies show wide disparities in incidence rates

Hib meningitis incidence: cases/100,000

- Hong Kong ('86)
- Thailand ('00)
- Vietnam ('03)
- Sri Lanka ('03)
- Mongolia ('03)
- Indonesia* ('02)

*yellow and green bars represent clinical meningitis prevented by vaccine
Hib - An important cause of pneumonia, True burden difficult to measure

- Culture-pos. Hib disease
- Culture-neg. x-ray confirmed pneumonia

Can be seen by surveillance for invasive disease or vaccine trials

Can be measured by vaccine trials (‘vaccine probe’)

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Hib - La partie connue ne reflète pas l’ampleur du problème

Courtesy Dr Kone, Mali EPI
Advocacy – Creating a Sense of Urgency

Creating opportunities for discussion

Asking key stakeholders for a plan

Learning from other champions
Advocacy – Need for champions

“Why do you need twin towers? Build one and get me the money for my children to get Hib vaccines!”

Dr Narimah Awin, Director, Family Health, Malaysia MOH
Generating interest and commitment: Recognizing cost of delay/vaccine opportunity

<table>
<thead>
<tr>
<th>Country</th>
<th>Deaths Averted/Yr (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>6,800</td>
</tr>
<tr>
<td>Kenya</td>
<td>4,500</td>
</tr>
<tr>
<td>Malawi</td>
<td>3,000</td>
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Vaccine introduction- the role of researchers

Traditional Roles
• Conducting research studies
• Publishing data
• Conferences, Expert groups

Additional roles:
• Publishing in non-scientific venues
• Support advocacy efforts as needed:
  – Garnering support of medical societies
  – Local politicians
  – Civil society groups
Analytic models possible but difficult – A recent analysis (Shearer J et al. PLoS 2009)

• 147 countries; 1990-2007

• Accelerated failure time model

• Controlled for economic, political, geographic, epidemiologic factors

• Key findings: Shortened time between vaccine licensure and decision associated with:
  – GAVI-eligibility
  – Presence of neighbouring adopters
  – Decreased vaccine price
  – Improved democracy score
  – Existence of long-term co-financing policies
### Assessing factors relevant for vaccine decision making - A review (Shearer J et al. PLoS, 2009)

<table>
<thead>
<tr>
<th>Author</th>
<th>Variables found important</th>
<th>Methods</th>
<th>Vaccine</th>
</tr>
</thead>
</table>
| **Widdus (1999)** | • Local disease burden and vaccine trial studies  
• Cost-effectiveness assessments  
• Cost reduction and knowledge sharing platforms for poorer countries  
• Cues to action such as international recommendations or private sector use  
• Social/Behavioural research to understand local barriers to acceptance  
• Advocacy for economic benefit of vaccine  
• Technology licensing that increases access of poor populations to vaccine  
• Coordinating approval process of vaccines in all countries  
• Mobilization of resources for immunization (from external sources for poor countries) | Conceptual framework of suggested actions to accelerate vaccine introduction in low-income countries | New vaccines |
| **Wenger et al. (2000)** | • Published burden of disease studies  
• Local experience with vaccine  
• National paediatric support  
• Price  
• Public interest (political will)  
• Effectiveness studies  
• Surveillance data | Qualitative interviews with country-level stakeholders and site visits in four early adopting, non-industrialized countries | Hib |
| **Miller & Flanders (2000)** | • DTP3 coverage  
• GDP per capita  
• Vaccine cost (price per dose)  
• Vaccine cost / per capita GDP  
• Treatment cost per unit  
• Years of Life Lost  
• Treatment cost prevented  
• Years of life saved | Cross-sectional, univariate logistic analysis | HBV |
<table>
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<tr>
<th>Study</th>
<th>Variables</th>
<th>Methodology</th>
<th>Vaccine</th>
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</thead>
<tbody>
<tr>
<td>Gauri &amp; Khalegian (2002)</td>
<td>Democracy score, Log GDP per capita, DTP3 coverage, Presence of UNICEF financing, PAHO revolving fund membership, Institutional quality score</td>
<td>Longitudinal multivariate logistic with coverage outcome and binary introduction outcome</td>
<td>HBV</td>
</tr>
<tr>
<td>DeRoeck et al. (2005)</td>
<td>Burden of Disease evidence, Cost-effectiveness information, Vaccine price, Vaccine safety and immunogenicity, Feasibility of local production, WHO recommendation, Ease of inclusion in current EPI schedule</td>
<td>Qualitative interviews with country-level policy makers and immunization professionals</td>
<td>Cholera, typhoid fever, shigellosis</td>
</tr>
<tr>
<td>Munira &amp; Fritzen (2007)</td>
<td>External pressures and advocacy, Disease burden evidence, Scientific support on benefit of vaccine, Feasibility of vaccine adoption into current EPI, Local vaccine pilot studies</td>
<td>Interviews and historical statistics to determine characteristics of two early adopting countries (Taiwan, Thailand)</td>
<td>HBV</td>
</tr>
<tr>
<td>Rossi et al. (2007)</td>
<td>Geographical region, DTP3 coverage, Previous introduction of HBV, GNI per capita</td>
<td>Cross-sectional, descriptive comparison</td>
<td>Hib</td>
</tr>
<tr>
<td>Danovaro-Holliday et al. (2008)</td>
<td>Political will, Disease burden and impact data, &quot;Experience exchange&quot; between countries, Affordability of the vaccine through the PAHO Revolving Fund</td>
<td>Descriptive statistics and programmatic lessons learned from the Americas</td>
<td>Hib</td>
</tr>
</tbody>
</table>
Importance of a strong & focused team
Lessons learned

• Plan for quality data early on
  • Program evaluation and impact assessment important

• Encourage use of available data (regional and global)

• Close coordination with various stakeholders essential

• Need to answer questions re: financing and supply

• Put vaccines in context of country policy needs

• Don’t assume everyone know

  • Advocacy and local champions needed to change perceptions about disease burden, value of vaccine

• Consistent messaging from partners is key

• Issues management planning is Important
Hib in EPIs, 2010: >150 countries, 60 (85%) GAVI countries have introduced and almost all eligible ones decided to introduce
Uptake in introduction has been accelerated for Hib vaccine in GAVI eligible countries.
Need to accelerate Pneumococcal Vaccine Introduction in Developing countries

PCV Access as of September 2009
Map courtesy of PneumoADIP

Pneumonia deaths in children > 5
1 Dot = 1,000 deaths

- Widespread or Universal Use
- In Routine Immunization for
- GAVI Introduced
- GAVI Approved Application
- GAVI Applied
- Expressed Interest
Where am I?

You must be a researcher

Because what you told me is absolutely correct but completely useless

Yes, how did you know?

You’re 30 metres above the ground in a balloon

Yes. How did you know?

You must be a policy maker

Because you don’t know where you are or where you’re going, and now you’re blaming me....
Need to coordinate with all Stakeholders

A coordinated approach from various stakeholders builds stronger support and more sustainable decisions.
Conclusions

• Many challenges for evidence-based decisions in developing countries, but focused strategies to accelerate new vaccine introduction can be effective: “Catalyst effect”

• No “standard process” for decision making, but approach strengthens country systems and decision making process

• Delay in introducing new vaccines to developing countries is unjustifiable: many obstacles, mostly surmountable by close coordination between various stakeholders and good communications
References

• Mahoney RT, Maynard JE. The introduction of new vaccines in developing countries. Vaccine, 1999;17: 646-52


• Progress in vaccination against Hib in the Americas. PloS 2008;5:e87
