TMH TO THE GATES FOUNDATION: HOW SMALL TOWN ROOTS LEAD TO BIG TIME SOLUTIONS FOR TROPICAL DISEASE

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Neglected Infectious Diseases
Bill & Melinda Gates Foundation
Overview

- A bit about my story from TMH to the Bill & Melinda Gates Foundation
- The story of Japanese encephalitis (JE) and India
- The next challenge- Neglected Infectious Diseases
My job at PATH

- Strengthen routine immunization
- Prepare for Rota vaccine introduction
- Strengthen YF immunization
- Prepare for Hib vaccine introduction
- Support the development of GAVI country support and application processes
- And-Go to India and make some recommendations on JE
Go to India and make some recommendations on JE
Flaviviruses

- Positive ss RNA viruses
- 69 pathogens
- Vector and non-vector borne
  - Tick borne
  - Mosquito borne
- Cause disease in all age groups around the world
- Many epidemic diseases including yellow fever, Japanese encephalitis, dengue
Japanese Encephalitis (JE)

- Arbovirus
- Flaviviridae
- Mosquito vector
- Pig amplifying host
- Frequently seasonal distribution
Japanese Encephalitis Distribution

- Seen in Asia
- Children less than 15
- Vaccine available
Go to India and make some recommendations
Japanese Encephalitis Distribution

- Seen in Asia-
  - 3 billion at risk
- Children less than 15
  - Can see in different age groups based on intensity of exposure
- Vaccine available
  - Not available in most endemic countries
Transmission of JE in Asia, 1871-2000
JE virus movement in Indonesia to Australia

Slide from John McKenzie
JE Transmission Cycle

Source: Tsai, T.F., 1994
Slide from Dr PN Rao, Hyderabad
Different patterns of age distribution of cases

Distribution of encephalitis cases by age group
Andhra Pradesh, India, 2000

Distribution of encephalitis cases by age group
Nepal, 2004

Data supplied by Government of Andhra Pradesh
Data supplied by WHO, Nepal
Japanese Encephalitis

- Leading cause of viral encephalitis in Asia
- Leading neurologic infection in Asia
- 175,000 estimated (now 69,000) cases annually throughout Asia
  - severely under-reported
- 10,000 - 15,000 deaths annually (5-35% CFR)
- JE-related disability 30-75%
Japanese Encephalitis

- **Prodromal stage- 2-3 days**
  - high fever and headache

- **Acute encephalitis stage- 3-4 days**
  - change of consciousness
  - seizures
  - death
Japanese Encephalitis

- **Subacute stage- 7-10 days**
  - fever decreases
  - mild symptoms decrease
  - secondary infections

- **Convalescent stage- 4-7 weeks**
  - mild cases recover
  - slow improvement
JE Disability

- **Motor-**
  - fine motor (72%)
  - limb paralysis (44%)
  - abnormal movements (8%)

- **Behavior**
  - Aggressiveness (72%)
  - Uncontrolled emotion/impulsiveness (72%)
  - Attention deficit (55%)
  - Depression (38%)
JE Disability

- **Intellectual**
  - abnormal (72%)
  - retardation (22%)

- **Other Neurologic**
  - Memory deficit (46%)
  - Expressive aphasia (38%)
  - Epilepsy (20%)
  - Cranial nerve paralysis (16%)
  - Blindness (2%)
JE Diagnosis

- HI- Hemagglutinin inhibition
- IgM ELISA of CSF or serum
- RT PCR assay for CSF
- Several rapid diagnostics were being developed
- Viral isolation
JE Treatment

- No specific therapy
- Supportive care
  - airway management
  - seizure control
  - cerebral edema
  - fluids and nutrition
  - manage secondary infections
Under-reporting of Cases
JE Control Programs

- Mosquito control
  - spraying
  - bed nets
- Pig control
  - segregation
  - slaughtering
  - vaccination
- Vaccination
Step 1 - Learn from what has worked

Major events in JE vaccination in Thailand

Vaccine Trials

Chiangmai

KPP

Ratchaburi

Model Vaccination

Chiangmai

Chiangrai

Extended Vaccination Programs

EPI-based

Provinces

1970

1980

1990

1997

Year

Source: Division of GCD, CDC, MOPH
JE Vaccine

- Used to control disease in Japan, Taiwan, Thailand, Korea, China...

- Vaccine choice
  - Mouse brain derived- Beijing strain or Nakayama strain
  - P-3 Primary Hamster Kidney Cell inactivated
  - Live Attenuated- SA 14-14-2
  - In development- chimeric...
The 3 pillars of JE control

- Good Surveillance
- Strong Case Management
- Immunization
JE Surveillance and Control - what's broken

Person

Infection

asymptomatic

symptomatic

case

Human Vaccination

Vector control

Feedback Control Program

Compile and analyze

Case reporting

Laboratory confirmation

Syndromic detection
- So now what?
- Gotta do it!
JE Project at PATH (very condensed!)

- 37 Million dollars- build a team, work with WHO, vaccine developers, and countries
- Increased data for decision making-
  - Create surveillance network, development diagnostic
- Vaccine development-
  - Ensure available, affordable, safe, effective, simple to use
- Country Support-
  - advocacy, control planning, technical support, vaccine introduction planning
### JEProject Summary Timeline

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**Outcome:**

Safe efficacious single dose vaccine
Inexpensive public sector price with 20 year commitment for low resource endemic countries public sector use.
Live SA 14-14-2 JE vaccine

- 5 dose vials
- Lyophilized
- Subcutaneous injection
- Single dose, lifetime protection
- Inexpensive
- Simple right?
Countries are like patients and families

- Indonesia - complex, 17,000 islands
  - Couldn’t have JE

- Nepal - want to take care of the problem
  - Know the disease, have will but almost no resources
  - Oh yea, then there is the royal assignation, the coup and the Maoists

- India -
SKIPPING TO INDIA

Advice- remember everyone else failed
JE in India

- Evidence of JE virus in 1953 with first outbreak in 1973
- Cases reported from almost all States in the country

**Challenges**

- JE control under the National Vector Borne Disease Control Program
- India never introduced a new vaccine into their immunization system
- India uses vaccines made in India
- Domestic vaccine supply limited to ~200,000 doses (3 doses/child)
- No large scale injectable vaccine campaigns have ever been done
- JE affected areas in India some of the hardest to reach areas
**JE case count (1998-2005)**

- **Mean no. of cases (1998-2005) = 2819**
- **Mean no. of deaths (1998-2005) = 659**
Demand for saving lives

1. Public demand – “save lives”
2. State Governments: Demand for vaccine
3. Massive outcry from Press – Control the disease
4. Demand of the scientific community- Introduce JE vaccination on a wider scale.

This demand led to:
5. Consultation with experts & partners
Decision making process

State demand

Decision to act

Data review on disease

Review control measures

Summarize experience in and out of country

Product and availability

Strategy

Decision

Science

Recommendations

NTAGi endorsement

Licensing

Planning for implementation

Procurement

Administrative process

Program monitor and review

Decision to continue

It’s more than one decision
Review the Data

- 20 years of data – outbreaks; age group
- Lack of uniformity - quality and sensitivity
- Continuous yearly outbreaks

JE Control measures

- Vector control methods – little to no impact
- Focal immunization – not sustained; improper planning; temporary impact
- Immunization- Solid evidence of impact in two states (AP&TN)
Available vaccines products

- No JE vaccine pre-qualified by WHO
- Mouse brain derived vaccine
  - Limited supply; Poor compliance; High cost
- SA14-14-2 live attenuated
  - Evidence of impact;
  - Global Advisory Committee on Vaccine Safety (GACVS) statement on safety and efficacy issues;
  - Single dose (Nepal Experience);
  - ? Availability
Decision on use of SA14-14-2 JE Vaccine

- Scientific committee – Indian Council of Medical Research (ICMR) led
- Recommendations:
  - Use of SA14-14-2 vaccine
  - Concurrent clinical studies
  - Campaign +RI Strategy
- Consultation with WHO and partners
- Endorsement of National Technical Advisory Group on Immunization

Resources:
1. Vaccine safety and efficacy literature: China/ Nepal/ South Korea
2. Clinical study reports from CDIBP, China
Operational Strategy and Process

- Decision on use of SA14-14-2 JE Vaccine in 1-15 year olds followed by into routine immunization
- Licensing of the vaccine- Registration for marketing of the product for use in public health program in the campaign districts
- Budgetary provision out of the domestic budget through the Parliament and Planning Commission
- A public sector unit local agent, Hindustan Latex Limited (HLL), was appointed by GOI
India JE vaccine Introduction
A Historic Event

- Program planned and vaccine licensed in record time - 8 months
- First “foreign” vaccine introduced into routine immunization in India
- First new vaccine introduced by the Government of India
- First injectable vaccine campaign ever in India
- Record coverage in hardest to reach parts of India (routine coverage 26%)
Vaccination in India

- Started May 15th, 2006
- Over 9 million children vaccinated
- 4 states, 11 districts
- First phase of 5 year plan
- Very high coverage achieved
Live SA 14-14-2 JE Vaccine made in China for use in India by the Government!

The diluent and vaccine (5-dose vial)
Results!
Vaccination in India - behind the scenes
Long term commitment from the government

<table>
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About 120 million children have been successfully vaccinated in India

New commitment of ~400M $ to expand program to 62 more districts
Go to the Gates Foundation

- Bring the lessons from JE and what it took to other areas
- Look at new areas that could use some help
- I am a primary care doctor at heart, what have I seen and what needs to be done to support communities and fight poverty?
- Everyone focused on HIV, TB, and malaria
- What about the most common diseases? Diseases of poverty?
Neglected Tropical Diseases (NTD)

- Diseases of poverty that promote the poverty cycle
- Treatment and prevention have large health and welfare benefits
- Many tools exist and impact already being seen
- Improvements in strategy and some additional tools needed

Impact

By: Abu D. 2010
1.4 Billion infected

- Most prevalent infections of the world’s poorest people living on less than $1.25 per day

- Ascariasis 807 million
- Trichuriasis 604 million
- Hookworm 576 million
- Schistosomiasis 207 million
- Lymphatic Filariasis (LF) 120 million
- Trachoma 84 million
- Onchocerciasis 37 million

NTDs currently impact over 600 million children and those at risk includes 878 million school age and 335 million pre-school children
What can integrated mass drug administration (MDA) achieve?

- Treat the 7 most common neglected diseases for 50 cents per person per year!
- The rapid impact package prevents new infections and can reduce transmission
- Zithromax – treats trachoma infections but also has activity against diarrhoea, respiratory illness and malaria
- Praziquantel – treats existing schistosomiasis infections, prevents future morbidity
- Mectizan (ivermectin) – removes the symptoms and blocks transmission of onchocerciasis (river blindness) by killing microfilariae (mf), prevents itching and blindness
- Mectizan/DEC and albendazole – prevent transmission of lymphatic filariasis (elephantiasis) by killing mf, alleviates mf symptoms, provide ancillary benefits such as removal of STH, control of scabies and other parasites
- Albendazole and mebendazole- treats intestinal helminthic infections (STH) and decreased transmission
What is MDA? Mass Drug Administration

**MDA**

Conducted at community or school level (one part of a NTD Program)

Up to 4 drugs for 7 diseases
- Albendazole/or mebendazole, ivermectin /or DEC, azithromycin, and praziquantel
- STH, Trachoma, Schisto, Oncho, LF

Inspired by drug donations and historically through vertical implementation programs

**State of the field**

Due to dz overlap can delivery drugs at the same time to the community increasing impact and reach
- Demonstration of success and cost-effectiveness have led to increases in funding and resources

Drug donations are expanding and need equal investment in implementation to achieve public health targets
Integrated delivery platform

We have developed a flexible and functional delivery platform that is accessing some of the world’s hardest to reach populations

- Now we have the opportunity to see how this system can be used to deliver other public health interventions that are amenable to outreach programs
- This will not only increase the usefulness and impact of these programs but also create sustainability and demand for this platform as some of the NTDs are eradicated or eliminated
January 30th London

Uniting to Combat Neglected Tropical Diseases
Ending the Neglect and Reaching 2020 Goals

Secret is shared common goals and worthy targets

http://www.youtube.com/watch?v= EZ8rvOiKDuI&feature=youtu.be
Where we are now | Where we can get with existing tools and strategies | Where we can get with new tools and strategies

**Diseases Targeted For Elimination**
- Guinea worm
- Leprosy
- Lymphatic filariasis
- Blinding trachoma
- Sleeping sickness

**Diseases Targeted For Control**
- Schistosomiasis
- River blindness
- Soil-transmitted
- Chagas disease
- Visceral leishmaniasis
- So now what?
- Gotta do it!
- What do we need?

- Research
- advocacy
- Creative problem solving
- New tools
- MDA delivery
- Monitoring and evaluation
- 50 cents
Concluding thoughts

- Things that were “not possible” may just not have been done
- What is your passion? What problem do you see?
- You can fix it. It is basic primary care.
- Increasing mental health services,
- Decreasing polypharmacy in the elderly,
- Putting in your 2 cents for the next 50 cent solution.