Module on Childhood Diarrhea
Part 3 – History of a global health initiative

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Outline
• Early history leading up to discovery of ORS
• Emergence of the Control of Diarrhoeal Diseases Programme, led by WHO
• Where we stand now:
  – The new 7-point plan
  – Diarrhea in the context of the “new global health”
• Discussion

Listen for the BIG IDEAS
What were the game-changers?

Cholera remains a large public health problem, but it is not one of the top five causes of diarrhea in children

Cholera is an acute intestinal infection caused by ingestion of food or water contaminated with the bacterium Vibrio cholerae. It has a short incubation period and produces an enterotoxin that causes a copious, painless, watery diarrhea that can quickly lead to severe dehydration and death if treatment is not promptly given. Vomiting also occurs in most patients.

http://www.who.int/topics/cholera/about/en/index.html

The first paradigm shift: Cholera was caused by contaminated water.
The first epidemiologist: John Snow, 1854

Cholera Bed
Dehydration: how diarrhea kills

"The eyes and the cheeks are sunken, the face is pinched, the lips and the tongue are dry, the fingertips are shriveled ("washerwoman's hands"), and the voice is hoarse . . . If the skin if pinched, especially over the abdomen, the skin folds do not disappear for some time . . . The pulse pressure decreases and it becomes imperceptible on the radial arteries . . . The urine diminishes in quantity . . . Muscle cramps, principally of the extremities but also of the trunk, are common at this stage . . . In fatal instances, death often ensues on the second or third day of the disease . . ."

—a description of cholera, written in 1967

[Ref 11 in JN Ruxin. Medical History, 1994]

In infants, sunken fontanelle is an important sign of dehydration

Management of diarrhea before 1960’s

JN Ruxin. Medical History, 1994

- 1920’s: discovery that intravenous fluid therapy corrects severe dehydration
- Up to the 1950’s:
  - Parenteral electrolyte solutions
  - Blood transfusions
  - Fasting
  - Gradual refeeding after the “starvation” period
- Fasting was based on theory that the gut needed to rest and recover from injury.
- Infant stay in hospital was typically 1-2 weeks, in part due to malnutrition induced by therapy

Pediatricians worried that about diarrhea epidemics in hospital nurseries that “frequently developed a high case fatality rate with attendant unfavorable publicity.” (p 367)

Steps forward: human physiology

- Daniel Darrow, Yale University, 1949:
  - "Effective replacement of water and electrolytes in patients with diarrhea should be based on exact knowledge of change in composition of body fluids."
Steps forward: human physiology

- Robert Crane, Washington Univ, 1960:

> "I have recently been reassured that this formulation of sodium ion-coupled glucose transport in the intestine was the basis for the development by others of the simple glucose-sodium chloride solution taken by mouth that is used worldwide to treat victims of life-threatening diarrhea as in cholera. A practical development based on my little piece of basic research has saved thousands upon thousands of lives."

Steps forward: Cholera Research Labs
Philippines, India, E. Pakistan (now Bangladesh)

  - First trial of oral rehydration as an adjunct to IV rehydration, but based on faulty physiology. He thought that Cholera poisoned the Na pump.
  - No reference to Crane and others
  - The trial "failed" and Phillips became a pessimist and obstructionist to other research

Steps forward: Cholera Research Labs
Philippines, India, E. Pakistan (now Bangladesh)

- The Dacca group tried again, with success
  - A Na and glucose solution always lowered the net stool output (meaning net absorption) and a solution without glucose always increased it.

Steps forward: Cholera Research Labs
Philippines, India, E. Pakistan (now Bangladesh)

- A group in Calcutta, working concurrently improved the formulation

He [Dr Macken] got up and said “This is one of the most profound developments in the treatment of... cholera diarrhea this century”. And I remember being a little startled by that and surprise to myself... “yeah, maybe he’s right”. But we had come as it (before) in terms of this [being] a really amazing scientific finding and it was based on true physiology... we were also preparing ourselves for using it as an emergency measure when we ran out of IV fluids. We were not yet saying that this would be a great thing to put into a village. It seemed like this was something we could use as an emergency backup.”

The move to oral without IV

- New young investigators, Nalin and Cash assigned to Dacca, one year out of medical school (26 yrs old)
- First trial of intragastric RT resulted in high rates of over- and under-hydration
  - 1 liter of ORT given per hour, regardless of output
  - Phillips reacted strongly to the failure

The move to oral without IV

- Second trial of oral RT found good results.
  - IV used until stable pulse, then oral only.
  - IV kept connected, and Nalin slept in the hospital, due to concern and controversy
From hospital to village

- Henry Mosley, chief epidemiologist at Cholera Research Lab, Dacca (posted by CDC)
  - With great political negotiation and difficulty, obtained staffing and permission to try ORT in rural Matlab district, with Cash and Nalin in charge
- 1969 Matlab trial confirmed that
  - “some cholera patients could be rehydrated with oral therapy alone and that field staff could be trained to administer the therapy with ease.”

"The discovery that sodium transport and glucose transport are coupled in the small intestine so that glucose accelerates absorption of solute and water (is) potentially the most important medical advance this century." --The Lancet, editorial, August 5, 1978
ORS can be made at home without a sachet

However, current interventions promote use of ORS packets with much less variability

Still thinking about those big ideas?

From Bangladesh and India to the US

- In 1992, CDC issues its first statement recommending the use of ORS to treat diarrhea in American children
  - "In the United States, each child will have had 7-15 episodes of diarrhea by the age of 5 years, 9% of all hospitalizations of children less than 5 years old are associated with diarrhea, and 300-500 children die each year from this potentially preventable condition. This report on ‘The Management of Acute Diarrhea in Children’ is CDC’s first statement regarding the important use of oral therapy for rehydration and maintenance of children in the United States with dehydrating diarrhea, as well as for nutritional support."
  - http://www.cdc.gov/mmwr/preview/mmwrhtml/00018677.htm

*The formidable and persistent ignorance of the western medical establishment, which continues over 25 years after the discovery of ORT is phenomenal." (Ruxin, 1994, p.396)

Establishment of Diarrhoeal Disease Control at the WHO

- 1978: statement adopted by the World Health Assembly (quoted at right)
- 1980: Program for the Control of Diarrhoeal Diseases (CDD) founded
  - First WHO program to integrate health services with research
- 1986: combined with Program on ARI

WHO CDD Priorities

1980 Priorities
- Bacterial enteric infections (microbiology, epidemiology, immunology and vaccine development)
- Viral diarrhoeas (microbiology, epidemiology, immunology and vaccine development)
- Drug development and management of acute diarrhoea

Etiologies of Diarrhea

Overall, these studies showed no cause-specific characteristics that would significantly influence the approach to case management or prevention.
Shift in WHO CDD Priorities

1980 Priorities
- Bacterial enteric infections (microbiology, epidemiology, immunology and vaccine development)
- Viral diarrhoeas (microbiology, epidemiology, immunology and vaccine development)
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1986 Reorganization
- Case management (improving treatment)
- Microbiology, epidemiology, immunology and vaccine development, and technology to support it
- Epidemiology and disease prevention (evaluation and implementation of interventions, other than vaccines, to prevent diarrhoeal diseases)

Shift in WHO CDD Priorities

Diarrhea control represents one of the leading global health initiatives to address in an integrated way:
- Prevention and treatment
- Biomedical and social sciences
- Field work and laboratory work
- The entire health system, from family and front-line to hospital

Shift in WHO CDD Priorities

Also in the 1980’s:
UNICEF Campaign for Child Survival
- New director of UNICEF: James Grant
   - Extraordinary vision, and capacity to bring people together
- Dec 1982: launched the “child survival revolution.”
- Global immunization rates went from 15% to > 60%
- Culminated in 1990 World Summit for Children

Shift in WHO CDD Priorities

UNICEF’s GOBI:
- Growth monitoring
- Oral rehydration
- Breastfeeding
- Immunizations

Shift in WHO CDD Priorities

Intrauterine growth retardation
Being too short for your age

High Prevalence of IUGR, Stunting and Severe Wasting in Children Under 5

- 13 million babies are born each year with intrapartum growth restriction
- 1/8 million children are stunted; 32% of all children
- 19 million children are severely wasted

This baby is severely wasted, i.e. very thin. Very high risk of mortality, esp. from diarrhea (But not only diarrhea)
Strong link between breastfeeding, diarrhea and malnutrition

- What is optimal breastfeeding?
  - Initiate within 1 hour of birth
  - Exclusive breastfeeding for 6 months
  - Continued breastfeeding for at least 1 year

Based on 2008 data, promotion of exclusive breastfeeding could save more child lives than any other known health intervention.

Why is breastfeeding so great, especially for babies with diarrhea?

- Breast milk contains all essential nutrients
- Breast milk also contains immunological substances. Mothers protect babies from most diseases that the mother is exposed to.
- Breast milk is probiotic: it helps the baby establish a gut population of microbiota that are favorable to health.
- Breast milk is clean. It protects babies from environmental pathogens that enter other foods and liquids.
- Breastfeeding is economical.
- When babies have no appetite due to illness, they often refuse other foods, but will continue to breastfeed.
- Breastfeeding comforts a sick child.

Breastfeeding Terminology

- Exclusive breastfeeding: only breastmilk
- Predominant breastfeeding: only breastmilk, water, and teas
- Partial breastfeeding: breastmilk + other fluids and solids

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0-6 months</th>
<th>6-23 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusive breastfeeding</td>
<td>3.6%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Predominant breastfeeding</td>
<td>4.2%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Partial breastfeeding</td>
<td>3.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Non-breastfeeding</td>
<td>5.0%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Based on 2008 data, promotion of exclusive breastfeeding could save more child lives than any other known health intervention.

Lancet nutrition series, paper 1

- Why is breastfeeding so great, especially for babies with diarrhea?
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FIGURE 2 Risk of mortality of infants in Nepal by time of breastfeeding initiation (Kaplan-Meier survival curves)

The milk secreted in the first few days (colostrum) is golden in color, small in volume, and extremely rich in immune substances. Babies get about 1 teaspoon per feeding. Early initiation of breastfeeding is very important to infant survival in the first month. In this study in Nepal, babies who started breastfeeding in the first hour of life had 3-4 times lower neonatal mortality rates than babies who started after 2 days of life.

Expanded Programme on Immunizations (EPI)

- Vaccination schedule
- Intensive malaria control
- Malaria in W.H.E.
- Primary care at home
- Intensive vector control
- Health centres
- Hospitals
- Child and mother

www.ics.ch/matters_colds_print.htm
Road to Health Card, developed in the 1980’s

GOBI + Vitamin A supplementation: For child survival and diarrhea control
- Vitamin A is stored well in the liver, thus you can give it every 6 months
- Safe to give in doses >100 x the RDA
- Recommended for ALL children from 6 mo to 5 years

Why is vitamin A so important?
- Globally prevalent
- Key functions:
  - Maintain epithelia
  - Immune function
- Decreases overall mortality by ≈25%
  - By decreasing disease severity
  - Especially diarrhea

Epithelial tissue changes with progressing vitamin A deficiency
- Decrease in goblet cells (mucus-secreting)
- Loss of columnar structure, general loss of organization
- Increasing keratinization (scaly structure)

Leap forward to 2009
7-point plan
1. Treatment package
   - Low-osmolality ORS
   - Zinc
   - Appropriate feeding
2. Rotavirus vaccine
3. Exclusive breastfeeding
4. Vitamin A supplementation
5. Handwashing with soap
6. Household water treatment
7. Safe fecal disposal

Leap forward to 2009
What's new here?
7-point plan
1. Treatment package
   - Low-osmolality ORS
   - Zinc
   - Appropriate feeding
2. Rotavirus vaccine
3. Exclusive breastfeeding
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5. Handwashing with soap
6. Household water treatment
7. Safe fecal disposal
**Latest treatment guidelines (2004): Zinc along with ORS**

- Zinc 20 mg/d for 10-14 days
- Reduces duration of diarrhea
- Reduced duration of diarrhea in the subsequent 2-3 months

**Why is zinc so important?**

**Physiologic roles of zinc**
- Structural role
- Signaling and neuromodulation
- Redox reactions and antioxidation
- Enzymatic function
- Cell growth, development, proliferation
- Cellular respiration
- Carbohydrate, lipid and protein metabolism
- Mediation of apoptosis

**Possible roles in diarrhea**
- Promotes healing of gut epithelium through roles in cell growth, development and proliferation
- Essential for enzymes and signaling within the immune system
- Zinc losses are likely high in diarrheal efflux, and body has no stores of zinc. Therefore replacement is necessary

**Also in the new guidelines: Reduced Osmolality ORS**

- 1/3 less need for IV therapy
- 20% less stool output
- 30% less vomiting
- Safety and mortality prevention similar

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**IMCI is a set of interventions for child health and survival that includes:**
- health systems strengthening
- health worker training
- algorithms for recommended treatments, counseling, and referral
- specific interventions
For all sick children:

THEN CHECK THE CHILD’S IMMUNIZATION, VITAMIN A AND DEWORMING STATUS

IMMUNIZATION SCHEDULE: Follow national guidelines

<table>
<thead>
<tr>
<th>AGE</th>
<th>VACCINE</th>
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<tbody>
<tr>
<td>0-9 months</td>
<td>DTP (1) IPV (1) ORS (1)</td>
</tr>
<tr>
<td>10-11 months</td>
<td>DTP (2) IPV (2) ORS (1)</td>
</tr>
<tr>
<td>12 months</td>
<td>DTP + Hepatitis B (2) IPV (2) ORS (1)</td>
</tr>
<tr>
<td>24 months</td>
<td>DTP + Hepatitis B (3) IPV (3) ORS (2)</td>
</tr>
</tbody>
</table>

ROUTINE IMMUNIZATION:
- DTP: Given at 2, 4, and 6 months of age.
- IPV: Given at 2, 4, and 6 months of age.
- ORS: Given at 2, 4, and 6 months of age.

ASSESS OTHER PROBLEMS:

FOR ALL SICK CHILDREN WITH ANY GENERAL ILLNESS SEEK IS TREATED AFTER THE NAME OF APPROPRIATE MEDICINE AND OTHER TREATMENT.

How to integrate rotavirus?
Your turn: What were the big ideas?

I would include these:
- Cholera was caused by bad water
- Na-glucose cotransport
- Oral rehydration (not IV)
- ORS could be administered at home
- Babies with diarrhea did not need to be starved—quite the opposite!
- AT WHO: to integrate epidemiology and disease prevention into CDD—including social sciences
- Lifesaving role of breastfeeding, especially EBF for the first months
- Micronutrient supplements could prevent many child deaths

Where do we stand today?

- Child mortality from diarrhea has decreased:
  - 1980: 5 million child deaths
  - 2010: 1.5 million child deaths
- Essential interventions have incomplete coverage (UNICEF data, 2005-2008):
  - EBF to 6 mo: 37%
  - VA, 2 doses/yr: 62%
  - Use of ORS: 33%
  - Continued feeding: 69%
  - Zn with ORS: insufficient data to track
  - Rotavirus vaccine too new to have any data

Progress has stalled in past decade

Two factors commonly cited:
- Change in head of UNICEF from a champion of child survival (Jim Grant)
- Emergence of HIV/AIDS and diversion of funding

Early Childhood Deaths

As Donors Focus on AIDS, Child Illnesses Languish

By CELIA W. DUGGER

By CELIA W. DUGGER

Published: October 29, 2009

JOHANNESBURG — Diarrhea kills 1.5 million young children a year in developing countries — more than AIDS, malaria and measles combined — but only 4 in 10 of those who need the oral rehydration solution that can prevent death get it.

http://www.nytimes.com/2009/10/30/world/africa/30child.html?_r=2#