International perspective on cholera prevention and review of available vaccines

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Topics

- John Snow
- WASH
- Injectable cholera vaccines
- WHO approved oral cholera vaccines
- Live attenuated, oral cholera vaccines
- Summary and thanks
John Snow and Cholera Prevention

John Snow’s 200th Birthday

John Snow’s Cholera Map
Key Events

• Dr. John Snow, Physician
• Reverend Henry Whitehead
  – 40% of broad street pump drinkers fell ill
  – 10% of persons using other water sources fell ill
• Engineer Joseph Bazalgette builds sewer system carrying waste and surface water away from London
Henry and Joseph

Reverend Henry Whitehead

Engineer Joseph Bazalgette
Figure 2. Distribution of the cholera cases in the study area during the large outbreak (March and April 2010) in eastern Kolkata, India (the yellow points are the locations of the cholera cases, and the blue line is the canal and ward numbers are shown inside the ward boundary)
Significantly high (red) and low (blue) risk areas during one year of pre-vaccination period in the study area, Kolkata India
Despite impressive global gains, most countries are falling short on meeting their own national WASH commitments,

83% and 70% of countries reportedly falling significantly behind the trends required to meet their defined national access targets for sanitation and drinking-water, respectively.

Insufficient funding for operation and maintenance undermines the sustainability of services in a major way.
• Insufficient staff in place to operate and maintain sanitation and drinking-water infrastructure.
• Lack of supply-side technicians and skilled labour stands out as a key barrier to the sustainability of services.
• On average, 34% of primary schools and 25% of rural health-care centres lack improved sanitation facilities.

UN-Water Global Analysis and Assessment of Sanitation and Drinking-Water - 2012
World Access to Sanitation

Population with no access to sanitation\(^1\) in % of the total population, 2004

- More than 50% — Red
- From 31 to 50% — Orange
- From 5 to 30% — Yellow
- Less than 5% — Cyan
- Data not available — Gray

1. According to the definition of WHO and Unicef: Population having no access to a waste water or solid waste treatment infrastructure, well maintained toilets or linked to a septic tank.

Sources: World Health Organization (WHO) and Unicef, *Meeting the MDG drinking water and sanitation target*, 2006.
World Access to Potable Water

Sub-Saharan Africa and Oceania are not on track to meet the MDG drinking water target

- **ON TRACK**: Coverage rate in 2010 was >95% or was within 5% of the 2010 rate required to meet the target
- **PROGRESS BUT INSUFFICIENT**: Coverage rate in 2010 was between 5% and 10% of the 2010 rate required to meet the target
- **NOT ON TRACK**: Coverage rate in 2010 was the same or lower than the rate in 1990 or below 10% of the 2010 rate required to meet the target
- **INSUFFICIENT DATA OR NOT APPLICABLE**: Data were unavailable or insufficient to estimate trends or a progress assessment was not applicable

Progress towards the MDG drinking water target; 2010
This document replaces the position paper on cholera vaccines published in the *Weekly Epidemiological Record* in April 2001. Other recommendations from WHO for the control of cholera include treating cholera cases, implementing water and sanitation interventions, and mobilizing communities: these remain unchanged.

SAGE reached the following conclusions and made the following recommendations.

Cholera control should be a priority in areas with endemic cholera, since cholera outbreaks can disrupt health systems.

Given the availability of 2 oral cholera vaccines (one prequalified and the other pending prequalification) and new data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization with these vaccines should be used in areas where the disease is endemic and should be considered for use in areas at risk for outbreaks in conjunction with other prevention and control strategies. Vaccination should not disrupt the provision of other high priority health interventions to control or prevent cholera outbreaks. Vaccines provide a short-term effect that can be implemented for immediate response while the longer term intervention of water and sanitation improvements, that involve large investments, should always be put into place.
History of cholera vaccines

- 1884: Ferran produced parenteral killed cholera vaccine
- 1894: Haffkine - another injectable vaccine
- 1920s: Russell – injectable vaccine showing 80% efficacy over 3 months of follow up
- 1960’s: Parenteral whole cell vaccines found to be associated with transient protection, and required frequent boosters; reactogenic
- 1973: WHO removes cholera vaccines from recommended cholera-control measures
Injectable cholera vaccine - Cochrane review

- Randomized/quasi-randomized controlled trials comparing injected cholera vaccines with placebo, control vaccines, or no intervention in adults and children.
- 16 trials, involving over 1 million adults, children and infants, fulfilled the inclusion criteria.
- Efficacy of 48% (95% CI: 35% - 58%), significant protection for 2 years, even after only a single dose.
- Associated with more systemic and local adverse effects compared to placebo, but these were not severe or life-threatening.
WHO pre-qualified and available OCVs

Dukoral
- Killed whole cell vaccine + B (binding) subunit of cholera toxin
- Requires buffer (75-150 ml)
- 2 doses for age >5 yrs. and 3 doses for age 2-5 yrs.
- Vaccine efficacy of 60% sustained over 2 years
- High vaccine price, mainly for travelers
- Monvalent (O1)

Shanchol
- Killed whole cell vaccine (no cholera toxin subunit)
- Buffer is not required
- 2 doses for all age groups (1+)
- Low-cost
- Bivalent (both O1 and O139)
OCVs: Also provide herd protection

- Beyond direct vaccine efficacy, OCVs also provide herd protection

Effectiveness of OCVs - 1

- **Dukoral: Case-control study in Beira, Mozambique:**
  - 11,070 individuals completed 2 doses (57% of target population)
  - 84% (95% CI: 43,95; p=0.005) of protective effectiveness after 1 year of vaccination

- **Dukoral: Cohort study in Zanzibar:**
  - 23,921 individuals completed 2 doses (50% of target population)
  - 79% (95% CI: 47,92; p=0.001) of protective effectiveness after 14 months of vaccination
Effectiveness of available OCVs - 2

- ORC-Vax: Case-control study in Hue, Vietnam:
  - 2 phased implementation of OCV in 25 ‘communes’ – 13 in 1998 (group A) and 12 in 2000 (group B)
  - 118,703 (79% of target population) and 103,226 (75% of target population) individuals completed 2 doses in groups A and B respectively
  - 50% (95% CI: 9.63; p=0.02) of protective effectiveness after 3-5 years of vaccination

- ORC-Vax: Case-control study in Hanoi, Vietnam:
  - ~80% of the estimated 370,000 age-eligible (10 years and above) individuals received at least 1 dose
  - 76% (95% CI: 5.94; p=0.04) of protective effectiveness after 3-4 months of vaccination
Way forward for cholera vaccines

- Multidose vial
- Liquid
- Volume ≤1.5ml

Targeting:
- all adults (incl. pregnant)
- + children & infants >10weeks
- + high-risk population

- Protection >80%
  - Early onset (within week)
  - Life-long/ >5 years

- High immunogenicity, stimulating anti-colonizing & anti-toxic antibodies

- Storage at room temperature

- Inexpensive, affordable to developing countries (<$1/dose)

- Can be scheduled with routine EPI
- Meet WHO production criteria & PQ

- Bivalent (Classical/01 & 0139) strain
- Single/Oral
- No requirement of buffer
- Safe with minimum adverse events and no reverse virulence
- Long shelf life (>3 yrs) with VVM attached
Several players are developing live cholera vaccines internationally; however PXVX-0200, Cuban 638, VA1.3/VA1.4 and Peru-15 appear to be the most advanced in clinical development.
Summary

• Access to improved sanitation, drinking water and promotion of personal hygiene remain the mainstays for cholera control and prevention.

• Vaccination with oral cholera vaccines would be synergistic with WASH interventions.
Thank you!