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Cholera vaccines and recommended use

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Comprehensive Family Immunization Program

Topics

- Review of cholera vaccines
  - Two oral vaccines marketed globally
- Recommended uses by epidemiological setting
  - Endemic vs. epidemic (pre-emptive vs. reactive)
- Experiences of mass cholera vaccination
- Conclusions

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Key reference

- WHO's Strategic Advisory Group of Experts (SAGE) on Immunization reviewed topic in October 2009
- This review was basis to update and publish in March 2010 "Cholera vaccines: WHO position paper"
  - These position papers summarize essential background information
  - They are concerned with vaccine use in large-scale immunization programs and conclude with WHO's current position on use of vaccines in global context
  - They are reviewed by experts within and outside WHO and reviewed and endorsed by SAGE

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Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

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http://www.who.int/wer

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Cholera vaccines: WHO position paper

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with WHO's current position on the use of vaccines in the global context. The papers have been reviewed by a num-

Vaccins anticholériques: note d'information de l'OMS

Conformément à son mandat, qui est de donner des avis aux États Membres sur les questions de politique sanitaire, l'OMS publie une série de notes d'information régulièrement actualisées sur les vaccins et les associations vaccinales contre les maladies qui ont un impact sur la santé publique au niveau international. Ces notes portent essentiellement sur l'utilisation des vaccins dans le cadre de programmes de vaccination à grande échelle; elles résument les informations essentielles sur les maladies et vaccins et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation des vaccins dans le

http://www.who.int/wer/2010/wer8513.pdf

Injectable vaccine

- Injectable vaccine prepared from phenol-inactivated strains of *Vibrio cholerae*
- Still manufactured in a few countries
- Not recommended by WHO
  - Limited efficacy
  - Short duration of protection

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WHO 2010, *Wkly Epidemiol Rec* 85:120–121

Oral live-attenuated vaccine

- Oral live attenuated single-dose vaccine (CVD 103-HgR)
- No longer produced (Orochol™, Mutachol™)
- *Side comment:* some experts consider that only a single-dose vaccine would be useful for reactive outbreak response

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WHO 2010, *Wkly Epidemiol Rec* 85:120

Oral inactivated vaccines *

Whole-cell *V. cholerae* O1
w/ cholera toxin B subunit
(WC-BS)

Clinical trial in Matlab,
Bangladesh, 1985

Whole-cell *V. cholerae* O1
w/ *recombinant* cholera
toxin B subunit (WC-rBS)

Whole-cell *V. cholerae* O1 and O139
(WC)

mORCVAX™
Licensed in 1997 in Vietnam
Produced for local use only

Dukoral™ (Crucell)
Licensed in 1991 in Sweden,
since then in >60 countries
Primarily as travelers' vaccine

Shanchol™ (Shanta Biotech)
Licensed in 2009 in India
Intended for global market

* Formalin- and heat-inactivated whole cell vaccines that require 2–3 doses in primary immunization series.

DUKORAL® 2 x 1 dose
Oral cholera vaccine
Suspension and effervescent granules for oral suspension.
3 ml of suspension in a vial and 5.6 g of effervescent granules in a sachet.
Store at 2 °C – 8 °C (in a refrigerator). Do not freeze.
For oral use.
SBLvaccines.
SODIUM HYDROGEN CARBONATE
Effervescent granules for oral use 5.6 g
To be used with Dukoral.
Read the package leaflet before use.
SBL Vaccin AB, Sweden
Lot
Exp.
DUKORAL

℞
Killed Bivalent (O1 and O139) Whole Cell Oral Cholera Vaccine
Shanchol™
शैंनकोल
Suspension strictly for oral use
1.5 mL single dose vial
SHANTHA

Characteristics	Dukoral™	Shanchol™
WHO prequalification	Yes, in October 2001	No, process ongoing
Licensed ages	≥2 years	≥1 year
Number of doses for primary immunization	Ages 2–5 years: 3 doses Ages ≥6 years: 2 doses	2 doses
Interval between doses	≥7 days (but <6 weeks)	≥14 days
Booster	Ages 2–5 yrs: after 6 months Ages ≥6 yrs: after 2 years	After 2 years
Administration	Oral with bicarbonate buffer (75 ml for children aged 2–5 yrs; 150 ml for persons aged ≥6 yrs)	Oral
Food and water restrictions	No food or water 1 hr before and after vaccine ingestion	No restriction
Packaging	3 ml single dose vial + effervescent granules in sachet	1.5 ml single dose vial
Cold chain and other storage requirements	Storage at 2–8 °*C*; 68cm^3 packed volume per dose (DTP dose 3 cm^3)	Storage at 2–8 °*C*; unknown packed volume
Cost per dose (US$)	5.00	1.85

Protective efficacy of WC-BS and WC vaccines in Matlab clinical trial, Bangladesh, 1985

Follow-up time	WC-BS vaccine			WC-only vaccine		
	All ages	2–5 yrs	≥6 yrs	All ages	2–5 yrs	≥6 yrs
6 months	85% (56–95%)	100%	76%	58% (14–79%	35%	71%
1st year	64% (50–74%)	44%	76%	56% (39–76%)	36%	67%
2nd year	52% (30–76%)	33%	63%	55% (33–69%)	24%	73%
3rd year	19% (<0–46%)	ND	41%	41% (7–62%)	13%	61%

* B subunit added significantly to protection for first 9 months of follow-up.

Clemens at al. 1986, Lancet 19:124–7
Clemens at al. 1990, Lancet 335:270–3

Safety of oral cholera vaccines

- Dukoral and Shanchol considered safe vaccines
- In particular, for Dukoral
  - In clinical trials with 240,000 participants, adverse events similar in vaccine and placebo groups; included mild abdominal discomfort, pain or diarrhea, mainly attributed to buffer solution
  - In post-marketing surveillance in Scandinavia, only 63 adverse reactions associated with >1,000,000 doses of vaccine sold during 1992–2003

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WHO 2010, *Wkly Epidemiol Rec* 85:121–2, 124

Use of oral cholera vaccines: General principle

Vaccination should not disrupt provision of other time-tested, high-priority health interventions to control or prevent cholera outbreaks

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WHO 2010, *Wkly Epidemiol Rec* 85:127

Use of oral cholera vaccines: Endemic areas

- Cholera control should be a priority in areas where disease is endemic
  - Endemic when cases of fecal culture-confirmed cholera diarrhea occurred in ≥3 of past 5 years
- Oral cholera vaccines **should be used** in conjunction with other prevention and control strategies
- Vaccinating entire population not warranted, rather targeted at high-risk areas and groups
  - Preschool- and school-aged children
  - Pregnant women and people living with HIV
- Periodic mass vaccination probably most practical strategy

WHO 2010, *Wkly Epidemiol Rec* 85:127–8

Use of oral cholera vaccines: Areas with or at-risk of outbreaks

- Treatment, potable water/sanitation and communication mainstay of control measures
- As an additional control measure, local health authorities *should* consider pre-emptive vaccination and *could* consider reactive vaccination (emphasis added)
- Factors to consider: local infrastructure; thorough characterization of current and historical cholera situation; clear definition of areas to be targeted
- Vaccination should cover as many (eligible) people as possible and be conducted as quickly as possible

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WHO 2010, *Wkly Epidemiol Rec* 85:120

Selected experiences of mass vaccination with Dukoral™

Place	Year	Vaccination setting	Doses administered
Uganda (1)	1997	Pre-emptive in refugee camps	63,220
Beira, Mozambique (2,3)	2003–2004	Endemic urban area before yearly outbreak	98,150
Darfur, Sudan	2004	Pre-emptive in complex humanitarian emergency	103,000
Aceh, Indonesia (4)	2004	Pre-emptive post-tsunami	137,000
Zanzibar, Tanzania	2009	Endemic urban areas with high-risk groups	100,000

1) Legros et al. 1999, Bull World Health Organ 77:837–42
2) Lucas et al. 2005, NEJM 352:757–67
3) Cavailler et al. 2006, Vaccine 24:4890–5
4) WHO 2006, http://www.who.int/topics/cholera/publications/final_tsunami.pdf

Lessons learned from mass vaccination experiences with Dukoral™

- Significant logistical and operational challenges
  - Cold chain capacity for vaccine transport and storage, 2/3-dose schedule, vaccine preparation
  - Difficult to restrict vaccination to some eligible areas or population groups
- Possibly high costs in addition to vaccine purchase
  - Mozambique US$ 2 per fully-immunized person
  - Indonesia US$ 18 per fully-immunized person

Detailed and prolonged planning is key to successful vaccination

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New vaccine introduction

- Inherently, a country decision
  - In the Caribbean, historically based on consensus among countries/territories
- Should be evidence-based
  - Preventable burden of disease
  - Cost-effectiveness of vaccination
  - Financial and logistical sustainability

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Conclusions

- Only oral cholera vaccines recommended
  - One WHO-prequalified, one undergoing process
- Vaccination as additional prevention strategy that should never disrupt time-tested measures
- Permissive recommendation for pre-emptive vaccination conditional on local assessment
- Previous experiences highlight how mass cholera vaccination is a major commitment from planning to implementation
- Detailed and prolonged planning is key to successful vaccination
  - All components of immunization programs, such as cold chain, training and communication

Possible issues within Caribbean context

- Which potential benefits would cholera vaccination have if a cholera case was imported?
- Would marginal benefits justify investment of resources (not only financial)?
- Which new risks could vaccination create?
  - False sense of security
  - If vaccination restricted to limited areas/groups, communication to public
- If vaccination began, when to stop?

Thank you