Updated WHO position paper on cholera vaccines

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Epidemiology

- Cholera is spread mainly by faecal contamination of water and food and is closely linked to poor sanitation and lack of clean drinking water.
- The actual global disease burden is estimated to be 3–5 million cases and 100 000–130 000 deaths per year.
- Recently larger and more frequent cholera epidemics have occurred.
- New and more virulent variant strains of V. cholerae O1 El Tor are replacing the original El Tor in parts of Africa and Asia.
- Emergence of antibiotic-resistant V. cholerae strains causes concern.
Pathogen and disease

- **Vibrio cholerae** is a rod-shaped, non-invasive, mainly waterborne bacterium with >200 serogroups, of which only O1 and O139 cause epidemic disease. Serogroup O1 has 2 biotypes: El Tor and classical. New variant strains of El Tor are associated with more severe disease. Resistance to antibiotics is a problem.

- **V. cholerae toxin** causes massive loss of intravascular and extracellular fluids and electrolytes in the small intestine.

- **Cholera** is characterized by acute, profuse watery diarrhoea of one or a few days’ duration. In its extreme manifestation, patients may become severely dehydrated within 3–4 hours. Case fatality rates (CFR) are usually < 5%, but may be much higher in high-risk groups.

- **Rehydration** is the mainstay of treatment (aims for CFR <1%). Antibiotics are indicated for severe cases only.
Currently available cholera vaccines*

1) Dukoral (WC-rBS): a monovalent oral vaccine based on formalin and heat-killed whole-cells (WC) of *V. cholerae* O1 plus recombinant cholera toxin B subunit.

2) Shanchol and mORCVAX: bivalent oral vaccines based on serogroups O1 and O139; these vaccines are closely related, but formulated by different manufacturers.

*CVD 103-HgR : an oral live attenuated single-dose vaccine is no longer being produced. The injectable vaccine prepared from phenol-inactivated strains of *V. cholera* is still manufactured in a few countries, but its use has never been recommended by WHO.
Manufacturers’ recommended schedules

**Dukoral:** 2 oral doses ≥7 days (but <6 weeks) apart for all aged ≥6 years. For age group 2–5 years: 3 doses ≥7 days, but <6 weeks, apart. If 2\textsuperscript{d} (or 3\textsuperscript{rd}) dose not given within 6 weeks of the previous, restart primary immunization.

A booster after 2 years for individuals aged ≥6 years. If >2 years since previous dose, restart primary immunization. For age group 2–5 years, 1 booster every 6 months; if >6 months since previous dose, restart primary immunization.

**Shanchol /mORCVAX:** 2 oral doses 14 days apart for all aged ≥1 year.

A booster dose is recommended after 2 years.
Safety and efficacy/effectiveness

- Dukoral and Shanchol/mORCVAX are safe in all age groups for which the vaccines are licensed (≥ 2 years and ≥ 1 year, respectively).

- Dukoral and Shanchol/mORCVAX offer significant protection against cholera during the first two years after vaccination: The ranges of protective efficacy at 4-6 months, 1 year, and 2 years after vaccination are 86%-66%, 62%-45%, and 77%-58%, respectively.

- Induction of herd protection is shown for Dukoral and considered likely for Shanchol/mORCVAX.
Some characteristics of currently available cholera vaccines

- Dukoral induces efficacious short-term protection; 85% (95% CI 56-95%) overall, and 100% (95% CI 80-100%) in children aged 2–5 years at 4-6 months of follow up.

- Due to its B-subunit, Dukoral confers significant short-term protection also against enterotoxigenic *Escherichia coli* (ETEC).

- Shanchol /mORCVAX induce longer protection in children aged <5 years and do not require booster doses every 6 months.

- Unlike Dukoral, Shanchol /mORCVAX do not require a buffer or water for administration. Also, Shanchol /mORCVAX require less storage space.

- Omission of the B-subunit makes Shanchol and mORCVAX less expensive to produce.
WHO position on oral cholera vaccines

- Cholera control should be a priority in endemic areas.

- Given the availability of 2 oral cholera vaccines and data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, these vaccines should be used in conjunction with other prevention and control strategies in areas where the disease is endemic, and immunization should be considered also in areas at risk for outbreaks.

- Cholera vaccination should be used in conjunction with other interventions. Vaccination provides an immediate short-term response while the longer term interventions such as improving water and sanitation are put into place.

- Although all age groups are vulnerable to cholera, where resources are limited immunization should be targeted at high-risk children aged ≥1 year (Shanchol or mORCVAX) or ≥2 years (Dukoral).
Control of endemic cholera:
- Vaccination should be targeted at high-risk groups, often including preschool- and school-aged children, pregnant women and HIV-infected individuals. Countries may also consider vaccinating older age groups. Immunization of the entire endemic population is not warranted (risk assessment).

- Periodic mass vaccination campaigns are probably the most practical option for delivering cholera vaccines. Schools, health-care facilities, etc may be appropriate venues for such campaigns.

- Incorporating cholera vaccination into routine vaccination programmes is an alternative or complementary strategy to vaccination campaigns, for example to reach young children between campaigns.

- Documented duration of significant protection induced by current cholera vaccines is 2 years. Hence, initial vaccination with 2 doses should be followed by a booster every second year.
Control of cholera outbreaks:

- The mainstays of control measures during epidemics remain appropriate treatment of cholera patients, improvement of water and sanitation, and mobilizing communities.

- Pre-emptive vaccination may prevent outbreaks or the spread of current outbreaks. Predictive risk-assessment tools to help determine possible need for pre-emptive cholera vaccination should be finalized and field-tested as soon as possible.

- Reactive vaccination may be an additional control measure, depending on local infrastructure, the epidemiological situation, and identification of target areas and should be guided by the 3-step WHO decision making tool. The feasibility and impact of reactive vaccination in halting outbreaks should be documented and disseminated.
Surveillance

It is strongly recommended that surveillance for microbiologically confirmed cases of cholera be instituted and integrated in already existing surveillance systems/networks to measure the burden of disease and monitor the seasonality and the impact of vaccination and other interventions in high risk populations.