Full Submission for inclusion of an IVD category to the EDL

Survey response 1

Response ID
37

Date submitted
2019-01-14 15:37:47

Last page
8

Start language
en

Date started
2019-01-09 15:06:39

Date last action
2019-01-14 15:37:47

Identification

Please indicate your response ID (unique identifier given to your screening application)
86.0000000000

Name of organization supporting this application:
WHO

Please enter full applicant's name
David Olson

4. Typical Characteristics of IVD’s in each format in which tests in the test category are available

Please provide detailed description of test components (reagents/instrumentation (where relevant), methodology and labelling for each test format available

Typically come in kit form, 10-20 individually wrapped test strips, which may be enclosed in a cartridge, supplemented by support materials including: disposable pipette and test tube, dilution buffer. Fresh stool sample or rectal swab is combined with a small volume of diluting buffer. A dipstick may be directly inserted into the test tube containing the stool-buffer solution for incubation or the solution is transferred by pipette to be added to the recipient well of a cartridge based dipstick. The test sample is allowed to incubate at room temperature for 15-30 minutes and then interpreted. The lateral flow immunochromatography is intended to produce a control line, and in positive samples additional result line(s) for the presence of O1 and/or O139 appear.

Diagnostic accuracy: Please provide typical sensitivity, specificity, PPV, NPV) for each test format available. Note: Section 5 below request a summary of studies supporting performance criteria shown in this section.

sensitivity (93%–98%) and specificity (67%–96%), PPV: 70-100% NPV: 90-100% for the different versions of the test available.

Specimen types: Please provide the range of specimen types that can be used with each format for which the tests are available.
fresh stool, rectal swab
| Facility level: the kind of facility in which each test format is intended to be used. Include all that apply. [I: primary health care clinic with no laboratory] | Yes |
| Facility level: the kind of facility in which each test format is intended to be used. Include all that apply. [II: district/hospital laboratory] | Yes |
| Facility level: the kind of facility in which each test format is intended to be used. Include all that apply. [III: regional/provincial laboratory] | No |
| Facility level: the kind of facility in which each test format is intended to be used. Include all that apply. [IV: national reference laboratory] | No |
| User Skill level: minimum level of training the operator undergoes to effectively perform each of the test formats. | non-laboratory trained health care worker |
| Throughput: number of specimens tested at one time for efficient use of each test format. | single use |
| Time to result: length of time to report the result for each test format | 15-30 minutes |
| Environmental stability (temperature, humidity) and shelf life for each test format. [Operating] | 10-30 deg C |
| Environmental stability (temperature, humidity) and shelf life for each test format. [Storage] | 2-30 deg C, 18-24 months |
| Environmental stability (temperature, humidity) and shelf life for each test format. [Transport] | 2-30 deg C |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Biohazard] | Yes |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Comment] | biologic infectious waste until dry |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Toxic to humans] | No |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Comment] | |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Toxic to environment] | No |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Comment] | |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Plastic] | Yes |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Comment] | Cartridge, tube, and pipette are plastic |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Other] | |
| Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply. [Other comment] | |
5. Evidence summary
### Summary of laboratory evaluation studies covering reliability and reproducibility, analytical accuracy (sensitivity, specificity); and analyses of potentially interfering substances, cross reactivity, stability, sample type. All relevant studies should be reported, detailing the search strategy and eligibility criteria used, or providing a systematic review. Please indicate the organizations responsible for conducting each of the studies and provide links to full reports for each study.

While the names of cholera RDTs and the companies involved in their manufacture have changed over the years, the general strengths and weaknesses of the tests both in the laboratory and field setting have remained relatively constant, though with some products clearly improved and performing better in terms of reliability, reproducibility, and accuracy. The following is an abstract of the most complete and recent review article on cholera rapid diagnostic tests (RDTs). It provides a summary and analysis of both field and laboratory evaluations published in the last 20+ years.

**Review of Two Decades of Cholera Diagnostics – How Far Have We Really Come?**
Michael H. Dick, Martine Guillerm, Francis Moussy, Claire-Lise Chaignat

**Abstract**
Background: Cholera, an ancient scourge, continues to inflict high rates of mortality today. The rising incidence of epidemics in areas of poor sanitation and crowding highlight the need for better epidemic prevention and early response. Such interventions require the availability of rapid and accurate diagnostic techniques to trigger timely response and mitigate the scale of the outbreak. The current gold standard of bacterial culture is inadequate for rapid diagnosis, highlighting the overarching neglect of field diagnostic needs. This paper was written to support the World Health Organisation’s Global Task Force on Cholera Control mandated Cholera and diarrhoeal disease laboratory Network (CholdiNet) in devising a protocol for the validation of Rapid Diagnostic Tests (RDTs) for Vibrio cholerae. The status of diagnostic tools for Vibrio cholerae is assessed, describing products that have been commercialised over the last two decades and discussing their peer-reviewed evaluation.

**Method:**
Review of post-1990 peer-reviewed and grey literature on rapid diagnostic tests for Vibrio cholerae.

**Results:**
Since 1990, twenty four diagnostic tests have been developed for the detection of Vibrio cholerae in human faecal samples. Fourteen of these have also been described in the literature, with rapid chromatographic-immuno assays (CIA) featuring strongly. Polymerase chain reaction (PCR) assays maintain the ability to detect the lowest amount of bacteria; however CIAs achieve both low detection thresholds and high sensitivity and specificity, making them possible candidates for use in field conditions. Field and laboratory studies were performed in a wide range of settings demonstrating variability in performance, however only a few of these studies were sufficiently stringent, highlighting five RDTs that showed promise in field conditions; COAT, IP cholera dipstick, SMART, IP dipstick and Medicos. In light of non-independent reporting, the authors would like to see these five products undergoing additional studies, with further technical improvements if needed and commercial production. The authors hope that public health use of such a RDT in limited-resource field conditions on stool samples may contribute to effective reduction in cholera epidemic spread.


Link: [https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0001845](https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0001845)

A summary table of the results of laboratory-based evaluations can be found as Table S3 in the Supporting Information section of the on-line version. Included are the organization names responsible for each study reported. [https://doi.org/10.1371/journal.pntd.0001845.s003](https://doi.org/10.1371/journal.pntd.0001845.s003)

In addition to the above published review, the WHO requested a review of cholera RDT quality by an independent review by the Institute of Tropical Medicine led by Jan Jacobs to guide member states in their supply decisions. RDTs submitted by manufacturers in response to an RFI announced by the WHO in 2013 were included in the review. An internal report was delivered in June of 2015 but was not published (a copy will be uploaded here).

**Laboratory evaluation of a selection of rapid diagnostic tests for Vibrio cholerae**
Barbara Barbé and Jan Jacobs, Institute of Tropical Medicine
Report June 20, 2015

In summary, nine RDT products from four manufacturers were analyzed on several metrics including limit of detection of target antigen, test line characteristics, inter-lot variation, ease of use, and accuracy and completeness of use instructions.

**Products:**
<table>
<thead>
<tr>
<th>Standard Diagnostics</th>
<th>SD BIOLINE Cholera Ag O1/O139</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artron</td>
<td>VC O Combo Cassette Test</td>
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<td></td>
<td>VC O1 Combo Cassette Test</td>
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<td></td>
<td>VC O139 Cassette Test</td>
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<td></td>
<td>VC O1-O Cassette Test</td>
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<td></td>
<td>VC O1 Cassette test</td>
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<tr>
<td></td>
<td>VC O1 Strip Test</td>
</tr>
<tr>
<td>Span Diagnostics</td>
<td>Crystal VC</td>
</tr>
<tr>
<td>CTK Biotech</td>
<td>Onsite Cholera Ag Rapid Test</td>
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</tbody>
</table>

Highlights of analyses:
- **Diagnostic sensitivity**: Challenged with *V. cholerae* clinical strains, all but one product (VC O1-O Cassette Test) showed visible test lines when expected for each of the *V. cholerae* O1 Inaba and Ogawa strains (n= 5 each).

- **Analytical sensitivity (LPS)**: SD BIOLINE Cholera Ag O1/O139 and Crystal VC showed the lowest LOD when assessed with *V. cholerae* LPS extracts.

- **Analytical sensitivity (*V. cholerae* reference strains)**: SD BIOLINE Cholera Ag O1/O139, VC O139Cassette Test and Onsite Cholera Ag rapid test showed the lowest LOD when assessed with *V. cholerae* reference strains.

- **Analytical specificity**: None of the products showed visible test lines when tested with the competing non-*V. cholerae* strains, comprising *Vibrio* non-cholerae species and related genera as well as intestinal pathogens.

- There were no invalid test results.

- Inter-observer agreement was high (92%)

- Overall, the SD Bioline test was preferred when all criteria considered.
Summary of studies of clinical accuracy evaluating the test in patient pathways in clinical settings covering sensitivity, specificity, and predictive values. Full evidence of all relevant studies should be reported, detailing the search strategy and eligibility criteria used, or providing a systematic review. Please indicate the organizations responsible for conducting each of the studies and provide links to full reports for each study.

Interpreting clinical accuracy studies for cholera rapid tests published is complicated by the gold standard, which has historically been cholera culture which has its own limitations for clinical sensitivity. PCR is also used as a gold standard in more recent studies where the technique is available. Each of these tests have different assay target/requirements. Culture requires living bacteria and may be affected by delays in transport or prior antibiotic consumption by the patient while PCR detects DNA and cholera RDTs detect cell wall (LPS) antigen neither of which needs necessarily to be living.

From the same publication cited at the beginning of the above Lab analysis section, “Review of Two Decades of Cholera Diagnostics – How Far Have We Really Come?” by Michael H. Dick et al. a summary of the field evaluations of RDTs is available in an accompanying table, Table S3 in the Supporting Information. https://doi.org/10.1371/journal.pntd.0001845.s002

To summarize, all but one study used cholera culture as the gold standard (one PCR only, and one with DFA included).

Range of sensitivity: 58-100% (>90% in 14 of 17 studies)
Range of specificity: 60-100% (>90% in 10 of 17 studies)
Range of PPV: 63-100% (>90% in 5 of 11 studies)
Range of NPV: 84-100% (>90% in 9 of 10 studies)

3 rapid diagnostic tests included in the above review (SMART, Medicos Dip Stick and an Institut Pasteur (IP)) were also included in a study examining the role the skill level of the user in determining clinical accuracy. Note: the IP dipstick became Crystal VC and is still manufactured. WHO purchases both Crystal VC and SD Bioline currently.


Sensitivity ranged from 58-94%, with the highest sensitivity (94%) and least difference between field and lab technicians recorded with the IP dipstick (though specificity was low for both groups)

The authors concluded that the IP dipstick was the most appropriate rapid diagnostic assay for the detection of V. cholerae O1 in remote locations or refugee camp settings. It was found to be valid and easy to use by both field and laboratory technicians and does not require refrigeration, even for long-term storage.

Most recently, 3 current RDTs underwent field assessment in Haiti. The study was a retrospective review of diarrheal disease surveillance records in the Enteric Diseases Laboratory at the study site in Haiti between May 1st, 2014 and October 15th, 2015. All specimens that underwent both RDT testing and culture for identification of V. cholerae and had complete records were included in our data collection and analysis. All samples were processed by trained laboratory technicians.

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0186710

Background characteristics of RDTs in the study: Crystal VC, Artron and SD Bioline RDTs for cholera.

1. Crystal VC Dipstick Arkray Healthcare Pvt., India
   Rapid visual immunochromatographic test for qualitative and differential detection of V. cholerae O1 and O139 in stool.
   Reported Sensitivity 88 -100%
   Reported Specificity 61 - 87.3%

2. Artron Vibrio cholerae O139 and O1 Combo Test
   Artron Laboratories Inc., Canada
   Rapid, convenient immunochromatographic assay for the qualitative detection of either Vibrio cholerae O139 or O1 in human fecal samples or environmental water.
   Reported Sensitivity 99%
   Reported Specificity 99%

3. SD Bioline Cholera Ag O1/O139 RDT
   Standard Diagnostics Inc., South Korea
   Rapid, qualitative test for the detection of V. cholerae O1 and O139 antigens in human fecal specimens.
   Reported Sensitivity 95.4%
   Reported Specificity 94.1%
**Results:**

Crystal VC: % and 98%CI  
Sensitivity 98.6 (96.5-99.6), Specificity 71.1 (64.7-76.9), Positive Predictive Value 81.3 (76.8-85.2), Negative Predictive Value 97.6 (93.9-99.3)

Artron  
Sensitivity 98.6 (92.7-100.0), Specificity 69.1 (55.2-80.9), Positive Predictive Value 81.1 (71.5-88.6), Negative Predictive Value 97.6 (93.9-99.3)

SD Bioline  
Sensitivity 81.1 (75.6-85.8), Specificity 92.8 (88.4-95.9), Positive Predictive Value 92.9 (88.6-96.0), Negative Predictive Value 80.8 (75.2-85.6).

**Summary of evidence of the impact of using tests in clinical practice on diagnoses, treatment, and patient outcomes. Please summarise model based evaluations and empirical studies where available and provide links to full reports.**

There are no direct studies measuring the impact of cholera rapid diagnostic test use. There is expert opinion that the use of a point-of-care test for cholera helps provide an initial indication of the presence of toxigenic V. cholerae transmission and thus the dangers of a nascent cholera epidemic. In contexts in which cholera is most common, lab capacity and availability tends to be very limited and thus standard methods for cholera detection (i.e., culture and biochemical tests) are either unavailable or require several days for shipment analysis and results transmission. As cholera outbreaks are explosive and the only realistic means to extinguishing an outbreak before it spreads is to raise an alert and begin a rapid response intervention when there is a positive cholera rapid diagnostic test in an area known to be affected by cholera. If this potential has not been realized, it is not the fault of the test, but the cholera response system in place and the lack of guidance on most effective actions to take and the resources to implement them.

**Summary of available non-clinical data (appraisal of evidence of quality manufacturing, ease of use and test disposal) and links to any relevant references.**

Please see WHO internal report pages 19-20 (by Institute of Tropical Medicine), referenced above in Lab testing section. There is no link, but the paper is uploaded here.

There are otherwise, no collective review on these non-clinical factors as a stand-alone publication.

For field evaluations of specific RDTs, the following is available:

Performance and utility of a rapid diagnostic test for cholera: notes from Haiti, page 523

(J. Boncy et al. / Diagnostic Microbiology and Infectious Disease 76 (2013) 521–523)  

"The Crystal VC RDT was easy to set up and read and had good stability. Most of the test kits were stored at ambient temperature for Haiti and were found to be optimal for use when tested for quality assurance."

Similarly, in a field evaluation report in Guinea Bissau, Field evaluation of Crystal VC Rapid Dipstick test for cholera during a cholera outbreak in Guinea-Bissau, p1119

(J. R. Harris et al. Evaluation of a rapid test for cholera, Tropical Medicine and International Health volume 14 no 9 pp 1117–1121 September 2009)  

"All laboratory workers reported that the test was easy to perform and the directions were simple to follow."
6. Societal impact information

**Ethical issues:** please detail any important ethical consideration by the type of test and consequences

- none

**Equity and human rights issues:** please indicate if it reduces inequities or increase equity and accessibility

As the test is intended for point-of-care in peripheral health centers, and even for community health workers, the wide availability of cholera RDT would improve equity in having a tool that could benefit the community by providing evidence that a cholera outbreak is impending and that rapid protective measures could be effectuated. At present, the benefit potential is at the community level rather than the individual level.

**Acceptability:** please indicate the acceptability by patient or by health care worker, benefits and harms

- Patient acceptability is high, as stool specimens tend to be abundant and sample collection is non-invasive. Health care worker acceptability is high and the test is in high demand in cholera endemic zones.
- As stated, the benefits accrue at the community level as an alert for and monitoring of a cholera epidemic, where a rapid effective response would reduce risk of infection and harm to community individuals. It does not necessarily benefit individual patients, as the disease itself is treated as for every severe dehydrating bacterial diarrhea with appropriate rehydration and antibiotherapy as needed.
- Harm can arise when test results are strictly used for patient management decisions: if a patient has a negative test for cholera by RDT and is then refused admission to a cholera treatment site, it would deny the patient needed diarrheal therapy that could be life-saving, whether the negative test result was a false negative or true negative. This is a facility management issue as much as it is the test which is not close to 100% sensitive.

7. Budget and resources impact

**Summary of data on comparative cost and cost-effectiveness, if available**

- none
Resources and budget impact on health care systems, including specialized human resources, training, maintenance issues as available to support implementation.

As with other rapid diagnostic tests (i.e., malaria), there is the cost of the test ($2) itself, plus the supply chain system that is capable of monitoring and replacing stock. In addition, even though laboratory personnel are not required to perform the test, the front-line health care worker does need a session of training, job aids for use and interpretation, and test-result based actions. Unlike malaria rapid tests, cholera RDTs are not meant for individual diagnosis, rather to detect the possibility of toxigenic cholera transmission in an endemic community and monitoring of the outbreak during its course. Thus, annual use in terms of number of tests per year in an identified cholera hotspot (per 200,000 population) has been estimated (internally, End Cholera by 2030, Investment Case) between 50-100 tests. The cost per person living in a cholera at-risk zone (hotspot) is estimated to be < $0.01 per year.

As with other diagnostic testing, quality control/assurance must be included and surveillance of proper RDT use to insure most effective application of the test in a cholera surveillance system.

8. Environmental impact

<table>
<thead>
<tr>
<th>Please enter any relevant information</th>
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<tbody>
<tr>
<td>Cholera RDTs, like malaria RDT, generate infectious (but non-sharps) waste, and when a plastic cassette is a feature of the test, there is plastic waste as well. There are no toxic chemicals used or to dispose of. A used test and sample tube as well as sample collection device (swab or other) become non-infectious when fully dried. Again, the absolute number of tests used annually is relatively small and would pose no significant added medical waste management burden or impact.</td>
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9. Proposed (new/adapted) text for the EDL.

<table>
<thead>
<tr>
<th>Please enter any relevant information</th>
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<tbody>
<tr>
<td>Diagnostic test: Vibrio cholerae species containing the O1 or O139-specific lipopolysaccharide antigen.</td>
</tr>
<tr>
<td>Test purpose: to screen patients with acute watery diarrhea that present with the clinical case definition of cholera. A positive test should raise a cholera alert while the samples are sent for culture confirmation of toxigenic V. cholerae.</td>
</tr>
<tr>
<td>Assay format: RDT</td>
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<tr>
<td>Specimen type: fresh stool or rectal swab</td>
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<tr>
<td>WHO prequalified or endorsed products: none</td>
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<td>WHO supporting documents:</td>
</tr>
<tr>
<td><a href="https://www.who.int/cholera/task_force/Interim-guidance-cholera-RDT.pdf?ua=1">https://www.who.int/cholera/task_force/Interim-guidance-cholera-RDT.pdf?ua=1</a></td>
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<td><a href="https://www.who.int/cholera/task_force/GTFCC-Laboratory-support-public-health-surveillance.pdf?ua=1">https://www.who.int/cholera/task_force/GTFCC-Laboratory-support-public-health-surveillance.pdf?ua=1</a></td>
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Additional information and signature

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<th>Please provide additional information that you would like to be considered.</th>
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<tr>
<td>Through the electronic signature below, I acknowledge that I have provided appropriate information to support this submission. I acknowledge that WHO reserves the right to format and select the information provided as necessary and agree that the information is publicly disclosed by WHO. [Electronic Signature (type your full name to sign):]</td>
</tr>
<tr>
<td>David Olson</td>
</tr>
<tr>
<td>Through the electronic signature below, I acknowledge that I have provided appropriate information to support this submission. I acknowledge that WHO reserves the right to format and select the information provided as necessary and agree that the information is publicly disclosed by WHO. [Date (yyyy-mm-dd):] 14/01/2019</td>
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