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Progress on the development of rapid diagnostic tests for foodborne neglected zoonotic helminthiases: A systematic review

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ABSTRACT

Background: Foodborne Neglected Zoonotic Helminths (FNZH) are parasites of both economic and public health importance. They include *Taenia solium*, *Echinococcus granulosus* sensu lato, *Echinococcus multilocularis* and Foodborne trematodes (FBT). FNZH are earmarked for major interventions for control, elimination and eradication. This systematic review highlights the progress towards development of rapid tests for the diagnosis of FNZH since 2010 when they were listed as neglected tropical diseases.

Methodology: A systematic search was conducted in three databases, World of Science, Embase and PubMed using the same search phrase. The search produced 480 hits. Three studies from back referencing were included. Only 22 of these met the inclusion criteria. Data was extracted from these and presented qualitatively.

Results: Twenty-five rapid diagnostic tests were found to have been developed since 2010, eight for diagnosis of *T. solium* infections, eight for echinococcosis and nine for FBT infections. The rapid tests for diagnosing *T. solium* infections included six antibody detecting and two antigen detecting tests. They constitute a combination among them, with some tests providing qualitative, others quantitative results. Similarly, seven out of the eight rapid tests developed for Echinococcus infections were antibody detecting tests save for one loop mediated isothermal amplification test. All of them were qualitative tests. For FBT infections, nine rapid tests were described; two antibody and one nucleic acid detecting test for diagnosis of Fascioliasis; three nucleic acid detecting tests for Opisthorchiasis; one antibody detecting test for Paragonimiasis; and for Clonorchiasis, one antibody and one nucleic acid detecting test. The FBT infection rapid tests were all qualitative in nature.

Most of these tests have not undergone field evaluation in endemic areas where they will be used most.

Conclusion: This review describes the development and evaluation of rapid diagnostic tests, while highlighting the need for in depth validations of the tools to determine how well they can perform in endemic areas.

1. Introduction

Foodborne Neglected Zoonotic Helminths (FNZH) are a component of the Neglected Zoonotic Diseases (NZD), a subgroup of Neglected Tropical Diseases (NTDs) recognized by the World Health Organization ("WHO | Neglected zoonotic diseases," 2015). FNZH include *Taenia solium*, *Echinococcus granulosus* sensu lato (s.l.), *E. multilocularis* and Foodborne trematodes (FBT). *T. solium, E. granulosus* s.l. and *E. multilocularis* rank first, second and third, respectively, among the multi-criteria based ranking of important foodborne parasites. The various FBT collectively constitute a large score of important foodborne parasites in the same ranking (FAO/WHO, 2014). Collectively, the FNZH are reportedly responsible for 649,433 illnesses, 44,033 deaths, 2,837,363 years of life lost, 2,336,038 years lived with disability and 5,183,418 disability adjusted life years globally (DALYs) (WHO, 2015a).

The WHO has developed strategies for prevention, control, elimination and possibly eradication of FNZHs (WHO, 2015b). In order to track progress, implementation targets and milestones have been set for

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each disease. To measure progress towards these milestones, monitoring and evaluation and disease surveillance will be essential. As such, there will be need for optimal diagnostic tools throughout the implementation process in order to provide robust and credible evidence on the performance of specific interventions (Savioli, 2012). Besides, diagnostics are needed for individual patient care in resource limited settings. Currently, diagnostic tests for FNZH in humans vary from simple microscopy to advanced imaging and molecular techniques.

T. solium taeniosis is diagnosed routinely by classical methods of demonstrating parasite material, eggs, scolices or proglottids, in feces using a microscope. However, microscopy has low sensitivity and cannot differentiate the eggs of closely related *Taenia* spp. and poses high risk of infection (Allan and Craig, 2006; Mwape and Gabriël, 2014). Improved techniques such as copro-antigen enzyme-linked immunosorbent assay (ELISA), native and recombinant antigen based enzyme-linked immuno electro transfer blot (EITB) techniques are available but not commercialized for routine use (Allan et al., 2003; Deckers and Dorny, 2010). Real time polymerase chain reaction for taeniosis diagnosis has also been developed (Carabin et al., 2017). *T. solium* neurocysticercosis is routinely diagnosed by imaging (computed tomography (CT), magnetic resonance imaging (MRI)) supported by various serological methods principally antibody and antigen ELISA (B158/B60, HP10) and EITB. The lentil lectin purified glycoprotein (LLGP)-EITB is the test of choice (Deckers and Dorny, 2010; Del Brutto et al., 2017).

Diagnosis of cystic and alveolar echinococcosis is principally by clinical signs, imaging (ultrasonography (US)), MRI, magnetic resonance cholangiopancreatography (MRCP)), supported by serological methods such as, indirect hemagglutination, ELISA, latex agglutination and point of care tests (Brunetti and White, 2012; Tamarozzi et al., 2016).

Diagnosis of FBT is mainly by imaging (US, CT), parasitological methods, immunodiagnostic and molecular techniques. The main parasitological methods are detection of eggs in fecal samples using the Kato Katz method, formalin ether concentration method, dilution egg count and sedimentation techniques (Fürst et al., 2012). Fecal egg detection and worm recovery following treatment are the present “gold standard” for *Clonorchis* and *Opisthorchis* diagnosis (Johansen et al., 2015). Immunodiagnostic tests such as, intradermal test, indirect hemagglutination, indirect fluorescent antibody test, indirect ELISA are available. Molecular-based tests have also been developed though they are not routinely used (Fürst et al., 2012).

In most resource limited settings, simple diagnostic tests such as, microscopy can be used. However, besides the inherently low sensitivity and specificity, their throughput is limited for large epidemiological studies. The existing immune- and molecular diagnostic tests require expensive equipment, infrastructure and highly skilled personnel, all of which are very scarce in resource limited settings. The lack of robust, sensitive and specific diagnostic tests which are also cheap, easy to use and suitable for endemic areas is a recognized challenge (Le and Hsieh, 2017; Wu et al., 2017), and a call for simple and easy to use rapid diagnostic tests has been made (Schwarz et al., 2017). For taeniosis and cysticercosis, target product profiles have been developed, including rapid point of care (POC) tests as well as reference tests for confirmation (Donadeu et al., 2017; WHO, 2015c).

The objective of this study was to give an update of progress on the development of rapid diagnostic tests (RDT) for taeniosis/cysticercosis, echinococcosis and FBT in humans, by giving an overview of the currently available rapid tests, and summarizing their characteristics. Moreover, the operational suitability of commercialized POC tests for FNZH in endemic areas was assessed using a standardized score card (Lehe et al., 2012).

2. Methods

For the purpose of this study, RDT is defined as qualitative or semi-quantitative *in vitro* diagnostic medical device, used singly or in a small series, which involves non-automated procedures and has been designed to give a fast result (2009/886/EC). A POC test is defined as by the ASSURED criteria: (1) Affordable by those at risk of infection, (2) Sensitive (few false-negatives), (3) Specific (few false-positives), (4) User-friendly (simple to perform and requiring minimal training), (5) Rapid (< 30 min), (6) Robust (does not require refrigerated storage), and (7) Equipment-free delivered to those who need it (Peeling and Mabey, 2010; Wu and Zaman, 2012). This POC definition has only been applied to commercialized rapid tests for scorecard evaluation. For other tests, a definition based on target settings of deployment has been used.

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines in April 2018 (Moher et al., 2009). Information was collected on the development and evaluation of RDTs for foodborne neglected zoonotic helminths since 2010.

2.1. Eligibility criteria

2.1.1. Inclusion criteria

The eligibility of studies to be included followed the PICOS (population, interventions, comparison, outcomes and study design) criteria: (1) Population - Any rapid tests for diagnosing *T. solium* infections, Echinococcosis and FBTs in human populations that can be used in four target settings; home, community, clinic and peripheral laboratory (Pai et al., 2012), (2) Interventions (Index tests) – Any technology for rapidly diagnosing any of the three classes of FNZH using acceptable reference tests meeting the STARD (Standards for reporting diagnostic accuracy studies) quality assessment criteria, (3) Comparator – Reference tests, gold standard, in their absence, results of several tests for the same condition, (4) Outcome – Studies that have reported diagnostic accuracy, precision, diagnostic sensitivity and specificity, analytical sensitivity and specificity, (5) Study design - Study designs in single gate or two gate formats as well as those in early development but report parameters under outcomes above, and (6) Others - Studies in English from 1st January 2010 to date.

2.1.2. Exclusion criteria

Publications covering the following topics were excluded; (1) Publications regarding pathogens other than the FNZH described above, (2) Diagnostic tests that are not rapid for the diagnosis of the FNZH, (3) Non-human rapid tests for FNZH, (4) Editorials or review articles without original data.

2.2. Information sources

Information was obtained from online databases; PubMed, Web of Science and Embase.

2.3. Search

The search was conducted in all three databases on the 6th of April 2018. One search phrase was used in all three databases and read as follows;

(Point of care test OR POC OR rapid test OR rapid assay OR quick test OR lateral flow OR strip test) AND (taeni* OR cysticerc* OR Neurocysticerc OR teni OR echinococc* OR Cystic hydatidosis OR hydatid OR Alveolar echinococcosis OR Foodborne trematodes OR FBT OR Clonorchiasis OR Opisthorchiasis OR fascioliasis OR paragonimiasis OR Fasciola hepatica OR Fasciola gigantic OR liver fluke OR oriental liver fluke OR human fascioliasis)

Further hand searching and follow up of references was also done.

2.4. Study selection

Studies were selected according to the PRISMA guidelines. Firstly, duplicates were removed from the total publications searched for. The remaining publications were screened on title and abstract and those that did not meet the inclusion criteria were excluded. Publications were then read in full and those that met the inclusion criteria were included for data extraction.

2.5. Data collection process

Data was initially qualitatively obtained on all RDTs for the included FNZH and listed according to the parasites they detected. The performance characteristics of these tests were summarized. Then commercialized POC tests were selected and subjected to evaluation of operational characteristics using the standardized score card (Lehe et al., 2012). Data was extracted by one reviewer (CM) and verified by another (CT). Where there was disagreement, other reviewers were consulted.

2.6. Data items

The following data was extracted: index test, reference tests, diagnostic sensitivity (se) and specificity (sp), analytical sensitivity and specificity, cross reactions and when reported positive and negative predictive values (PPV/NPV), study design, population description, sample size, number of positive samples, number of negative samples, test indication, intended use, target population and setting, location of use, test format, portability, target analyte, sample type, steps to results, nature of results, result record and author as well as publication year (Fig. 1).

2.7. Risk of bias and quality of included studies

The risk of bias in individual included studies was assessed using the guidelines of the Agency for Healthcare Research and Quality methods guide for comparative effectiveness reviews (AHRQ) (Viswanathan et al., 2012) (Fig. 2). The quality of included studies was assessed according to the STARD guidelines (Cohen et al., 2016) (Fig. 3).

3. Results

3.1. Study selection

The search resulted in 480 titles and abstracts. After removal of duplicates, 288 titles were retained. Of these 215 titles were excluded for various reasons; 107 titles were not about the three groups of neglected zoonotic helminths, while the other 107 papers covered subjects other than diagnostic development/evaluation; one paper was in French. Seventy three (73) publications were selected for full reading. Fifty-one (51) publications were excluded due to other reasons: 46 publications covered NZH but not diagnostic evaluation while two were in Chinese and two in Arabic. One publication could not be accessed online. Finally, data was extracted from 22 publications.

3.2. Study characteristics

3.2.1. Risk of bias within studies

Assessment of risk of bias in individual included studies showed that, most studies were biased on selection of subjects. There was no

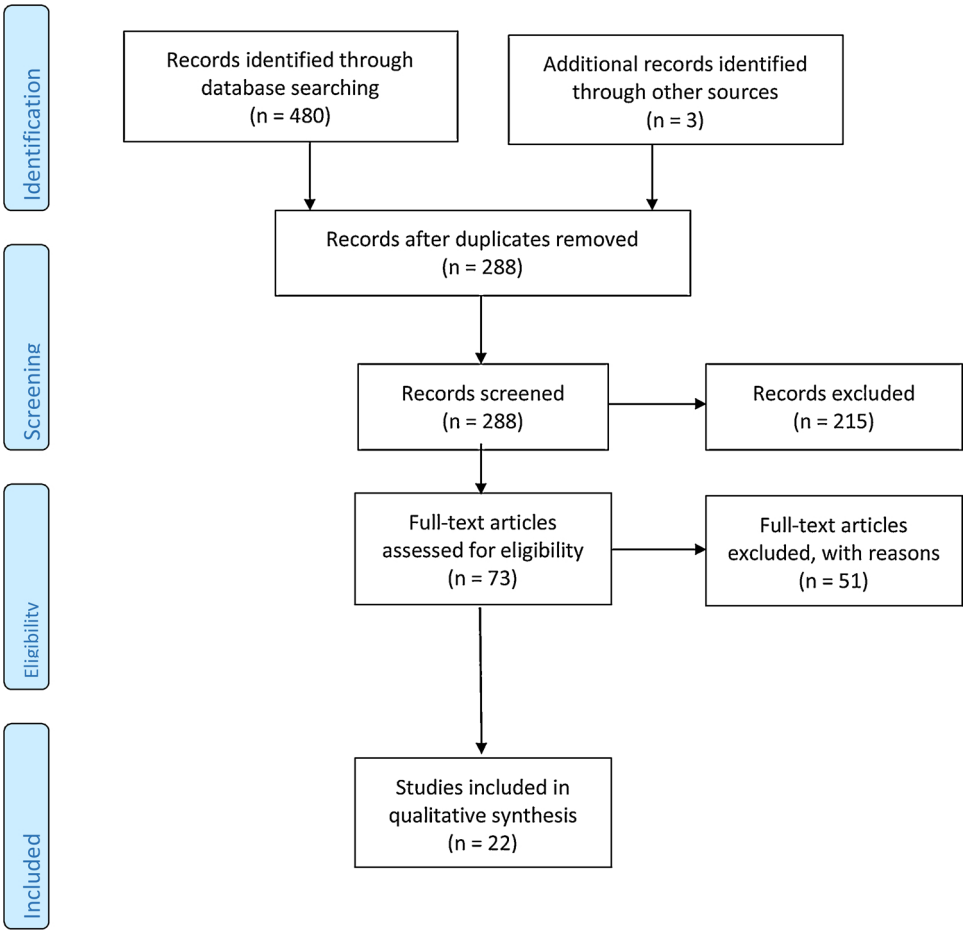

Fig. 1. PRISMA Flow Diagram.

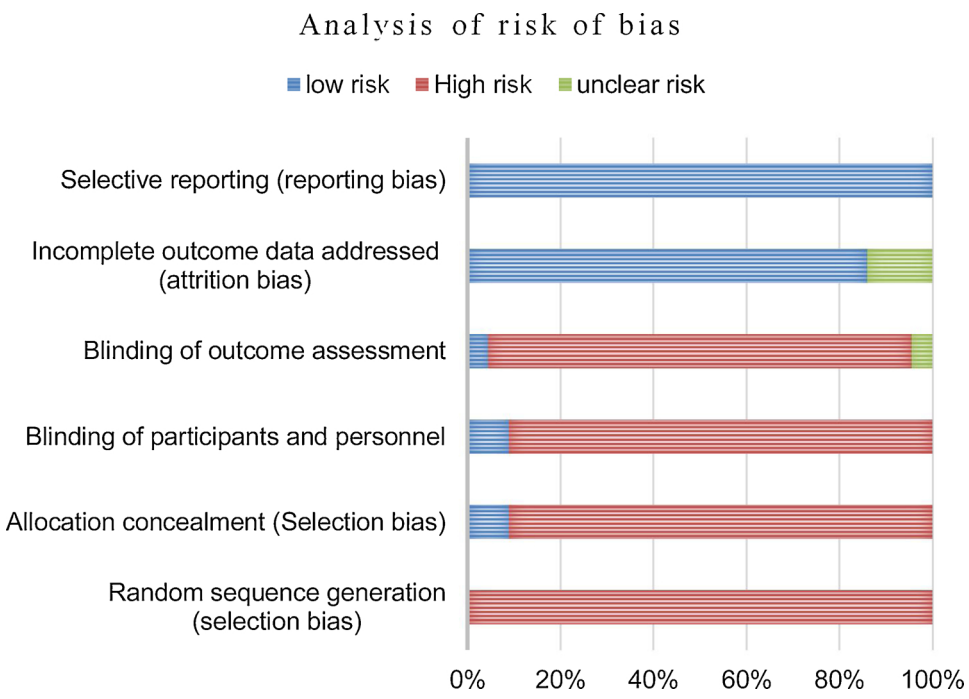

Fig. 2. Risk of bias in included studies.

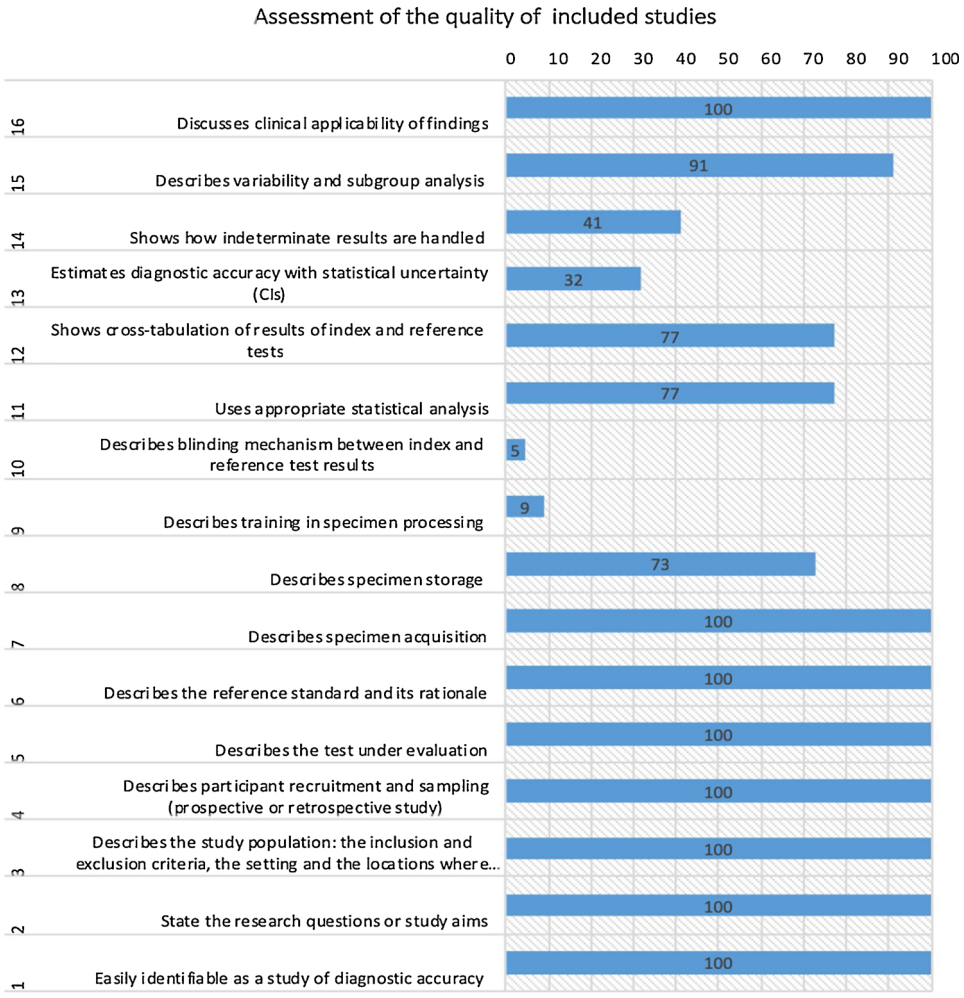

Fig. 3. Quality of studies included in the study based on the STARD checklist.

Table 1
Summary characteristics of rapid tests for *Taenia solium* infections in humans.

Disease	Taeniosis	Cysticercosis	Cysticercosis	Cysticercosis	Cysticercosis	Cysticercosis	(Neuro) cysticercosis	Neurocysticercosis
Index Test	**rES33-MICT (Magnetic immune-chromatography test)**	**rT24H-MICT**	**rT24H Quick ELISA™**	**rGP50 Quick ELISA™**	**sTs18var1 Quick ELISA™**	**UCP-rT24H-LFA**	**Slide/Latex Agglutination test**	**HP10 LFA**
Reference test	PCR, Morphological identification	Imaging (CT, MRI)	Imaging (CT, MRI), LLGP EITB	Imaging (CT, MRI), LLGP EITB	Imaging (CT, MRI), LLGP EITB	Imaging (CT, MRI)	Imaging (CT, MRI)	Clinical, Imaging, Cytochemical analysis
Diagnostic se %	94.5	93.9	96.3	93.5	89.8	96	64.7 (CSF), 52 (serum)	100
Diagnostic sp %	96	98.9	99.2	98.6	96.4	98	85.7 (CSF), 96 (serum)	100
Analytical se	–	Single cyst: 33 2 or more cysts: 93	Single cyst: 47.49(CDC*), 66.7 (Peru) Degenerating cyst: 50 (CDC), 52.5 (Peru) Calcified cysts: 52.6 (CDC), 59.4 (Peru)	Single cyst: 42.1(CDC), 41.7 (Peru) Degenerating cyst: 48.5 (CDC), 31.7 (Peru) Calcified cysts: 43.9 (CDC), 43.9 (Peru)	Single cyst: 15.8 (CDC), 20.8 (Peru) Degenerating cyst: 27.3 (CDC), 40 (Peru) Calcified cysts: 21.9 (CDC), 33.5 (Peru)	2 cysts or more	–	–
Analytical sp (Other diseases/ parasites being tested to evaluate specificity)	*Taenia saginata, Ascaris lumbricoides, Echinococcus granulosus* s.l., *Echinococcus multilocularis, Plasmodium falciparum, Schistosoma mansoni, Schistosoma haematobium, Trichinella* sp.	*Taenia saginata, Ascaris lumbricoides, Echinococcus granulosus* s.l., *Echinococcus multilocularis, Plasmodium falciparum, Schistosoma mansoni, Schistosoma haematobium, Trichinella* sp.	*A. lumbricoides, E. granulosus* s.l., *E. multilocularis Entamoeba histolytica, Fasciola* sp., *Giardia lamblia, Hymenolepis nana, Hepatitis C virus, Heterophyes, P. falciparum, S. haematobium, S. mansoni, T. saginata, Toxoplasma gondii, Trichinella* sp., *Undefined infections*	*A. lumbricoides, E. granulosus* s.l., *E. multiloculari,s E. histolytica, Fasciola* sp., *G. lamblia, H. nana, Hepatitis C virus, H. heterophyes, P. falciparum, S. hematobium, S. mansoni, T. saginata, T. gondii, Trichinella* sp., *Undefined infections*	*A. lumbricoides, E. granulosus* s.l., *E. multilocularis, E. histolytica, Fasciola* sp., *G. lamblia, H. nana, Hepatitis C virus, H. heterophyes, P. falciparum, S. hematobium, S. mansoni, T. saginata, T. gondii, Trichinella* sp., *Undefined infections*	Same as rT24H-MICT	–	–
Cross reactions	*A. lumbricoides, E. granulosus* s.l., *P. falciparum, S. mansoni, Trichinella* sp.	*A. lumbricoides, S. mansoni*	None reported	None reported	False positives recorded on controls from non-endemic areas	*Schistosoma, T. spiralis, H. nana, Paragonimus westermani*	Tubercular meningitis	–
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective, cross sectional	Retrospective
Population description	Hospital referrals for all studies							
Sample size	439	396	1318	1318	1318	313	31 CSF, 98 serum	80
Positive samples	161	115 (100, ≥2 viable cysts, 15 single cyst)	704 from two sites CDC (307) and Peru (449) segregated as follows: 282 ≥ 2 viable cysts, 43 single cyst, 186 degenerating, 269 calcified cysts	704 from two sites CDC (307) and Peru (449) segregated as follows: 282 ≥ 2 viable cysts, 43 single cyst, 186 degenerating, 269 calcified cysts	704 from two sites CDC (307) and Peru (449) segregated as follows: 282 ≥ 2 viable cysts, 43 single cyst, 186 degenerating, 269 calcified cysts	63 samples each with 2 or more viable cysts	17 CSF (5 clinical suspects, 12 proven cases), 48 serum (25 clinical suspects, 23 proven NCC)	60 (34 active NCC, 26 inactive NCC)
Negative samples	164 (145 USA, 19 Egypt)	164 (145 USA, 19 Egypt)	362 (98 USA, 16 Egypt, 248 Peru)	362 (98 USA, 16 Egypt, 248 Peru)	362 (98 USA, 16 Egypt, 248 Peru)	170 (78 USA, 92 Netherlands)	14 CSF, 25 serum	–
Heterologous infections	117	117	252 (CDC only)	252 (CDC only)	252 (CDC only)	80 from previous studies	25 serum	20
Test format	Lateral flow assay using magnetic particles as detection system	Lateral flow assay using magnetic particles as detection system	ELISA	ELISA	ELISA	Lateral flow assay using up-converting phosphor reporter particles	Slide agglutination	Lateral flow assay using carboxyl-modified latex microspheres

(*continued on next page*)

Table 1 (*continued*)

Disease	Taeniosis	Cysticercosis	Cysticercosis	Cysticercosis	Cysticercosis	Cysticercosis	(Neuro) cysticercosis	Neurocysticercosis
Sample type and quantity	Serum, 5 µL	Serum, 5 µL	Serum, 5 µL	Serum, 5 µL	Serum, 5 µL	Serum, 40 µL of diluted sample	Drop of CSF/ serum	CSF
Time to results (Minutes)	25	15	60	60	60	30	2	10
Reference	(Handali et al., 2010a)	(Handali et al., 2010a)	(Lee et al., 2011)	(Lee et al., 2011)	(Lee et al., 2011)	(Corstjens et al., 2014)	(Biswas and Parija, 2011)	(Fleury et al., 2016)

Abbreviations: MICT-magnetic Immunochromatography test, UCP- up converting phosphor reporter PCR- Polymerase chain reaction, CT- Computed tomography, MRI- Magnetic resonance imaging, LLGP EITB- Lentil-lectin purified glycoprotein enzyme-linked immuno-electro-transfer blot, CSF- Cerebrospinal fluid, CDC- Centre for disease prevention and control of Atlanta, PPV- Positive predictive value, NPV-Negative predictive value, ELISA- Enzyme-linked immuno-sorbent assay, NCC- Neurocysticercosis.

randomization in selection of subjects or concealment of cases. Most were case control studies while others, especially nucleic acid detecting tests, were mainly laboratory based using DNA serial dilutions. One had a component of field evaluation as a minor part. Less than 10% of the studies reported blinding of laboratory analysts, or blinding of the interpreters of reference results (Fig. 2).

3.2.2. Assessment of quality of included studies

The quality of included studies was acceptable according to the STARD guidelines (Cohen et al., 2016). All studies were easily identifiable as diagnostic accuracy studies, stated the research questions or aims, and described the population, participant recruitment and sampling, reference standard, rationale, specimen acquisition and discusses clinical applicability of the findings. There were notable omissions in some studies; the majority of studies did not describe mechanisms of blinding and training in specimen processing, did not show how indeterminate results were handled and did not report diagnostic accuracy results with statistical uncertainty (Fig. 3).

3.3. Synthesis of results

3.3.1. Rapid diagnosis of Taenia solium infections in humans

Data about rapid diagnosis of *T. solium* infections in humans was retrieved from five studies, including diagnostic tests for taeniosis (1), cysticercosis (5) and neurocysticercosis (2), summarized in Table 1. Additional test characteristics have been summarized in Supplementary Table 1. In total, eight RDTs have been developed.

3.3.1.1. Antibody detecting tests. Several tests targeting antibodies against native and recombinant antigens have been developed. The ***rES33-*** Magnetic immune-chromatographic (***MICT)*** test detects antibodies against adult *T. solium* excretory secretory proteins (TSES) (Table 1) in serum using a recombinant protein in a magnetic labelled detection system to improve sensitivity and to quantify the results of the test. (Handali et al., 2010a). The diagnostic performance of rES33 in this test format compares well with *T. solium* native excretory secretory antigens (se 95% and sp 100%) (Wilkins et al., 1999) and the rES33 antigen (se 99.4, sp 93.9%) in an EITB format (Handali et al., 2010b). The rES33 antigen has been found to cross react with serum of *A. lumbricoides, E. granulosus* s.l.*, P. falciparum, S. mansoni* and *Trichinella species* patients (Handali et al., 2010b, 2010a), hence the lower specificity. This test meets most of the target product profiles in the minimum criteria of a POC test proposed by the WHO for diagnosing taeniosis save for the fact that, it targets antibodies and not antigens as suggested (Donadeu et al., 2017). The limitation of this test is that it still uses a liquid conjugate and therefore requires a cold chain and a reader. The bench top magnetic reader also makes it less portable to use as a POC test in endemic areas (Handali et al., 2010a). Despite this, it can be used at clinic level.

Several tests have been developed targeting antibodies against the previously described recombinant T24H (rT24H) glycoprotein (Hancock et al., 2006) in serum for cysticercosis diagnosis. The ***rT24H-MICT test*** uses the same technology as the rES33-MICT; therefore, the advantages and the disadvantages are similar. The ***Up-converting phosphor reporter rT24H lateral flow assay*** (UCP-rT24H LFA) uses Up-converting Phosphor (UCP) particles as a detection method (Ouellette et al., 2009). The results are read using a multi strip reader after chromatography and when the strips are dry. In this format, this test has been reported to detect low amounts of antibodies (Corstjens et al., 2014). The ease of use is reduced by the requirements of sample dilution, washing, conjugate application and strip analysis. This limits its use to begin at the level of the clinic. The rT24H antigen has been used in other test formats with reported sensitivity and specificity as follows; Multi antigen print immune assay (MAPIA), 97% and 99%, and EITB 94% and 99%, respectively. A cross reaction with *Schistosoma mansoni* has been previously reported in the MAPIA test format (Rodriguez et al., 2012).

Table 2
Summary characteristics of rapid tests for *Echinococcus granulosus* s.l. and *E. multilocularis* infections in humans.

Disease	Alveolar/Cystic echinococcosis	Alveolar echinococcosis (AE)	Alveolar /Cystic echinococcosis	Cystic echinococcosis (CE)	Cystic echinococcosis (CE)	Cystic echinococcosis (CE)	Cystic echinococcosis (CE)
Index Test	**Dot immune-filtration gold (DIGFA)**	**rEM18-ICT (ADAMU AE)**	**HCF-rEM18-ICT(Immuno-chromatography test)**	**AgB-Dip stick**	**rAgB8/1-ICT (ADAMU CE)**	**AgB-Ag5_ICT (VIRapid hydatidosis)**	***NADH* 1-LAMP**	**rAgB-ICT (hyd rapid)**
Reference test	Imaging (Ultrasound, X-ray, CT, MRI)	ELISA, Immunoblot, Imaging (MRI)	Clinical, imaging, ELISA	Imaging (Ultrasound, X-ray, CT), pathology, serology	Surgical, serology	Indirect Haemaglutination, ELISA	Surgery	Ultrasound
Diagnostic se %	Hospital CE: 80.7, AE: 92.9 Community: CE 94.6, AE 97.1	94	CE 91 AE 98	IgG4 95 IgG 100	78	94.7	–	64
Diagnostic sp %	Hospital CE: 93.4 (AgB), AE: 90.3 (EM2)	95.4	CE 96.9 AE 99.3	IgG4 100 IgG 87.5	89.8	99.5	–	86–100
Analytical se	–	–	–	–	Single cysts 78.8% Multiple cysts 76.5%	–	10fg	–
Analytical sp (Other diseases/parasites being tested to evaluate specificity)	*Simple cystic disease, carcinoma, tuberculosis, space occupying lesions, cirrhosis, abscess, cysticercosis, cholecystitis/ gallstones, other patients*	*E. granulosus* s.l.	Serous hepatic cysts, cysticercosis, schistosomiasis, toxoplasmosis, paragonimiasis, clonorchiasis	Malaria, toxocariasis, strongyloidiosis, ascariasis, fascioliasis, taeniosis	*E. multilocularis, Clonorchis sinensis, T. solium, T, saginata, Paragonimus miyazaki, P. westermani, Schistosoma hematobium, Spirometra erinacei*	–	*Cysticercus bovis, Fasciola gigantica, Schistosoma bovis*	–
Cross reactions	AgB in AE, EM2 in CE, cysticercosis	None reported	*T. solium* cysticercosis	Toxocariasis, fascioliasis	*E. multilocularis*	–	None reported	None reported
Study design	Retrospective, cross sectional	Retrospective	Retrospective	Cross sectional	Retrospective	Retrospective	Cross sectional	Retrospective
Population description	Hospital referrals	Hospital referrals	Hospital referrals	Hospital referrals	–	–	Hospital referrals	Hospital referrals
Sample size	Retrospective1602, Prospective 3191	94	322	53	206	276	100	87
Positive samples	Retrospective: 857 CE, 42 AE Prospective 160 CE, 108 AE	50 AE	195 (144 CE, 51 AE)	21	50	77	100 cysts (50 camel, 40 cattle, 10 human)	60
Negative samples	35	20	60	15	88	199	Nucleic acid free water	25
Heterologous infections	702	24	67	17	68	–	Present, number not mentioned	2
Test format	Multiple antigen immune-filtration assay	Immuno-chromatography	Immuno-chromatography	Immuno-chromatography	Immuno-chromatography	Immune-chromatography	Loop mediated isothermal amplification test	Immune-chromatography
Sample type and quantity	Serum 20 μL, heparinized blood 40 μL	Serum 10 μL	Serum 10 μL, heparinized blood 20 μL	Serum 10 μL	Serum 10 μL	Heparinized blood, serum 30μL	Cyst DNA	Serum 7μL
Time to results (Minutes)	4	20	15	15	20	30	60	15
Reference	(Feng et al., 2010)	(Sako et al., 2011, 2009)	(Wang et al., 2013)	(Khalilpour et al., 2014)	(Santivañez et al., 2015)	(Delgado et al., 2010)	(Ahmed et al., 2016)	(Vola et al., 2018)

Abbreviations: HCF- Hydatid cyst fluid, ICT- Immunochromatography test, NADH-Nicotinamide adenine dinucleotide, LAMP- Loop mediated isothermal amplification, AE- Alveolar echinococcosis, CE- Cystic echinococcosis.

Quick ELISA™ has been adapted for sero-diagnosis of cysticercosis based on the recombinant T24H and GP50 glycoproteins as well as synthetic peptide sTs18var1 (Table 1). As such, it is suitable for exposure surveillance of cysticercosis. Quick ELISA™ is a high throughput quantitative assay which can be performed on the bench top but can also be automated. It is suitable for field studies but requires a basic laboratory due to; the number and type of samples, the buffers it uses which require a cold chain and equipment such as, the absorbance reader which requires electricity (Lee et al., 2011). The performance of the rGP50 in other test formats, sensitivity and specificity; EITB 90% and 100%, ELISA 95% and 94%, MAPIA 93% and 100%, is close to the minimum requirement of 90% and 98%, respectively. False positives reported for the rGP50 have not been linked to any particular parasitic infections (Bueno et al., 2005; Rodriguez et al., 2012). The performance, sensitivity and specificity, of the Ts18var1 in other test formats reported are; EITB, 97% and 100%, ELISA 95% and 85%, another ELISA 90% and 90%, FAST ELISA 97% and 100%. There are no cross reactions reported in other test formats on the rGP50 and sTs18var1 (Rodriguez et al., 2012). The Quick ELISA seems to be a good test for use at the periphery laboratory.

All the antibody detecting tests meet the minimum performance requirements for cysticercosis diagnosis of sensitivity 90% and specificity 98%, proposed by the WHO in the target product profiles for human cysticercosis, only tests based on sTs18var1 fall short (Donadeu et al., 2017). The Quick ELISA rT24H showed the best performance among the antibody detecting tests but for the detection of NCC, the Se drops when the number of cysticerci is low.

3.3.1.2. Antigen detecting tests. The ***Rapid Slide/Latex Agglutination test*** has been standardized and evaluated for the detection of *T. solium* metacestode antigen in cerebral spinal fluid (CSF) and serum (Table 1). It uses latex particles which have been sensitized by rabbit produced hyper immune cysticercosis anti-serum. The agglutination is performed on a glass slide where the latex suspension is added to a serum or CSF sample. A positive test is seen by agglutination. Cross reactions with tuberculous meningitis on both serum and CSF were reported. One healthy control out of 25 serum samples tested positive (Biswas and Parija, 2011). The test results were below the performance requirements suggested for cysticercosis and NCC (Donadeu et al., 2017). Nevertheless, the simplicity of the test format makes it easy for single case diagnosis. Preparation of the latex suspension and sensitization of latex particles are relatively easy, moreover they can be stored at 4 °C for further use. This test can be deployed at clinic level for serum, and hospital for CSF, the limitation being the needed expertise to obtain CSF by lumbar puncture.

Another RDT reported for NCC is the ***HP10*** LFA (Table 1) (Fleury et al., 2016). The target analyte is the HP10 antigen in CSF, which is a circulating surface as well as excretory secretory antigen in *T. saginata*, *T. hydatigena, T. solium* and *E. granulosus* s.l. (Harrison and Parkhouse, 1989). The main purpose of this assay is post treatment monitoring in patients with extra parenchymal NCC as well as supportive diagnosis given that imaging is less sensitive for extra parenchymal NCC. The HP10 antigen has been used in ELISA format for NCC diagnosis using CSF and serum with sensitivity and specificity of 91.3% and 100%, and 84.8% and 98%, respectively (Fleury et al., 2007). The diagnostic performance meets the suggested requirements for cysticercosis diagnosis. Further evaluation is needed using patients with multiple parasite infections. The largest limitation of this test is the sample type. Despite the test being easy to perform, the lumbar sampling procedure is invasive and requires expertise. Therefore, the lowest level of deployment of this test is the hospital.

3.3.2. Rapid diagnosis of Echinococcus granulosus s.l. and Echinococcus multilocularis infections in humans

Data was extracted from eight publications about rapid diagnosis of *Echinococcus* spp. infections due to *E. granulosus* s.l. which causes cystic echinococcosis (CE) and *E. multilocularis*, which causes alveolar echinococcosis (AE). The data has been combined for both diseases and summarized in Table 2. Additional test characteristics have been summarized in Supplementary Table 2.

3.3.2.1. Antibody detecting tests. Several rapid tests targeting antibodies to native and recombinant antigens for *E. granulosus* s.l. and *E. multilocularis* have been developed (Table 2). There are tests specific for CE or AE, and combined tests for CE and AE. A number of tests for CE diagnosis based on antigen B antibodies have been developed. The ***Antigen B lateral flow dipstick (AgB-LF Dipstick)*** was evaluated for rapid diagnosis of CE. The test format requires multiple dipping steps of the stick in diluted serum, conjugate and wash buffer, limiting its use to clinic level. The test cross reacted with fascioliasis and toxocariasis patients sera (Khalilpour et al., 2014). The ***rAgB8/1-ICT (ADAMU-CE, ICST corporation, Japan)*** is a commercialized immune-chromatography lateral flow test based on recombinant antigen B (Santivañez et al., 2015). Its test sensitivity was reported better on patients with liver cysts compared to patients with lung cysts. A study which compared the performance of three commercial tests (DIGFA (Unibiotest, China), ADAMU-CE (ICST corporation, Japan), VIRapid (Vircell, Spain)) for CE diagnosis reported the sensitivity of rAgB8/1-ICT to be 57% (Tamarozzi et al., 2016), which is lower than previously reported (Table 2). In this comparison study, VIRapid was the best performing followed by DIGFA, then rAgB8/1-ICT in the diagnosis of CE (Tamarozzi et al., 2016). Like the other two tests, the performance varied with cyst stage and was good in viable cyst stages CE2-CE3 though poor in CE1 and non-viable cyst stages C4 and C5. The specificity was lower (89.8%) in studies including AE patients and higher (100%) without AE patients. However, it is still a simple test useable at community level. The ***Antigen B and Antigen 5 Immuno-chromatography test (AgB-Ag5-ICT)*** (the commercial name is ***VIRapid hydatidosis***) is a lateral flow test based on the most immunogenic purified antigens of *E. granulosus* s.l., AgB and Ag5, (Sarkari and Rezaei, 2015) developed in 2010 (Delgado et al., 2010). It detects antibodies against these two antigens. It has been evaluated as a screening and diagnostic test (Tamer et al., 2015). The average diagnostic sensitivity reported varies; 94.7% (Delgado et al., 2010), 96.8% (Tamer et al., 2015), 74.1% (Tamarozzi et al., 2016), 82.3% and 80% in a large scale evaluation using both retrospective and prospective study designs (Baraquin et al., 2017), and most recently 69% (Vola et al., 2018). Sensitivity has been shown to vary with cyst stage and status. The test sensitivity is best in viable stages CE2-CE3b and poorer for CE1 and the inactive stages of CE4 and CE5. Similarly, its specificity has been reported to range from 80.9% to 100%. The test is deployable at community level. Another ***rAgB-ICT*** based rapid test has been developed to detect antibodies against antigen B of *E. granulosus* s.l., based on a similar dipstick format as the AgB-LF dipstick (Vola et al., 2018), also deployable at clinic level.

Some rapid tests have been developed for differential/concurrent diagnosis of CE and AE, rendering them specifically relevant for use in co-endemic areas (Table 2). The ***Echinococcosis Dot Immuno-Gold Filtration Assay (DIGFA, Unibiotest, China)*** is a commercialized rapid test based on the specific *E. multilocularis* EM2 antigen and three *E. granulosus* s.l. antigens: AgB, EgCF (partially purified cyst fluid) and EgP (protoscolex). The DIGFA was tested on hospital samples as well as on samples from community-based surveys (Feng et al., 2010). It is a POC deployable at community level. Another differential immune-chromatography test (ICT) design, the ***HCF-rEM18-ICT***, uses two antigens, hydatid cyst fluid (HCF) for *E. granulosus* s.l. and the recombinant EM18 for *E. multilocularis* (Wang et al., 2013). Important to note is that the antibodies against the rEM18 antigen cross reacts with HCF antigens, though at a very low level (Knapp et al., 2014; Wang et al., 2013). The simplicity of this test makes it suitable for community deployment.

Some developed tests are specific to AE diagnosis (Table 2). **The *rEM18-ICT (Immunochromatography, ADAMU-AE)*** is a

commercialized test for diagnosis of *E. multilocularis* based on antibodies against an 18 kDa antigen (Em18), one of the products of cysteine peptidase on ezrin-radin-moesin like protein. The rEM18-ICT was evaluated for rapid clinical diagnosis (Sako et al., 2009), post treatment follow up (Sako et al., 2011) and reliability as a first screening test (Knapp et al., 2014). In the 2014 study, the reported sensitivity was 90% and specificity of 92.7%. The evaluation studies have reported cross reactions with CE, human liver cysts, toxocariasis and hepatic carcinoma (Knapp et al., 2014; Sako et al., 2009). This test is suitable for community deployment.

Antibodies against CE and AE antigens have been reported to cross react with each other and with various parasitic and non-parasitic conditions. Feng (Feng et al., 2010) demonstrated cross reactions between CE and AE of about 35% and that AgB, EgCF, EgP and EM2 all cross reacted with *T. solium* cysticercosis. Other studies have reported that EgCF, AgB and Ag5 cross reacts with *Toxocara*, *Trichomonas*, malignancies, serous cysts and *Leishmania* (Sarkari and Rezaei, 2015). Antibodies against the EM2 antigen also cross react with the HCF antigens though at a low level (Knapp et al., 2014; Wang et al., 2013).

3.3.2.2. Nucleic acid detecting tests. The loop mediated isothermal amplification (LAMP) test for CE, ***NADH-1 LAMP-CE***, is based on the mitochondrial NADH dehydrogenase subunit 1 gene (Ahmed et al., 2016). It was designed for postsurgical confirmation of CE using DNA extracted with a commercial kit. The results are visualized by color change of the included dye. The test showed no cross amplification with DNA from *T. saginata* cysticerci, *Schistosoma bovis* and *Fasciola gigantica* (Ahmed et al., 2016). *E. multilocularis* DNA was not included in the controls. The test performance is comparable to the ultrasound threshold for abdominal CE. However, its usefulness is limited due to the fact that it needs cyst DNA as sample. The DNA extraction step confines its use to laboratories and near hospitals where such surgical procedures to remove cysts can be performed.

The diagnostic performance of tests for echinococcosis are normally compared with ultrasound, which is the "best generally available" diagnostic test. In community studies, it has been reported with sensitivity range of 88–98% for abdominal CE and AE. The specificity ranges between 93–100% for both conditions (Macpherson and Milner, 2003). Only three rapid tests have reported performance comparable to this threshold; HCF-rEM18 ICT, AgB lateral flow dipstick and the LAMP CE.

3.3.3. Rapid diagnosis of foodborne trematode infections

Data was extracted from nine publications: three publications for *Fasciola* spp. (3 tests), three for *Opisthorchis* spp. (3 tests), two for *Clonorchis* spp. (2 tests), and one for *Paragonimus* spp. (1 test). Data is presented according to the parasite species in Table 3. Additional test characteristics have been summarized and presented in Supplementary Table 3.

3.3.3.1. Human fascioliasis. Three rapid diagnostic tests for human fascioliasis have been developed, two antibody and one nucleic acid detecting test (Table 3). The ***recombinant pro-Cathepsin L1-serofluke (rpCL1-serofluke)*** test uses recombinant pro-cathepsin L1 and targets antibodies against Cathepsin, a cystein protease, for sero-diagnosis of fascioliasis caused by both *Fasciola gigantica* and *F. hepatica* in low resource settings (Martínez-Sernández et al., 2011). There were no cross reactions reported. Similarly, other studies have also not found cross reactions on cathepsin-based ELISA (Gonzales Santana et al., 2013), and reported good performance (Sarkari and Khabisi, 2017). The dipstick format which uses diluted serum and blood as samples does not allow easy distribution and operation by non-technical community health workers. The ***Excretory-Secretory (ES)-dip stick*** is similar in format to the rpCL1-serofluke but detects antibodies against Fasciola ES antigens which cross react with Schistosomiasis (Ali, 2012). The ***Intergenic spacer (IGS)-LAMP*** was designed to differentially amplify extracted DNA for *F. hepatica* and *F. gigantica* from fecal samples. It did not amplify DNA from other parasite species included in the evaluation (Ai et al., 2010). The DNA extraction step, and the use of a water bath limits the infrastructure level of use. All tests for human fascioliasis are suitable for use at peripheral laboratory level.

3.3.3.2. Human opisthorchiasis. Three nucleic acid detecting tests were found for *Opisthorchis viverrini* infections (Table 3). All the tests use extracted parasite DNA as a sample. The ***Mito (Mitochondria)-LAMP*** is based on *mitochondrial nicotinamide hydrogenase gene (nad1)* (Le et al., 2012). The ***internal transcribed spacers 1(ITS1) - (ITS1-LAMP)*** was developed for diagnosis of *O. viverrini* (Arimatsu et al., 2012) but it amplified DNA for *Opisthorchis felineus* and 5 other stool samples which were considered negative on microscopy (Arimatsu et al., 2015, 2012). The ***OVMS (Opisthorchis viverrini microsatellite) - LAMP*** is very specific and also a thousand times more sensitive than the ITS1-LAMP. Its analytical specificity was also better, other parasite DNA tested were not amplified (Arimatsu et al., 2015). The complexity of LAMP, especially the DNA extraction step limits its use to peripheral laboratories.

3.3.3.3. Human clonorchiasis. The ***Cytochrome C oxidase subunit 1 (cox1)-LAMP DNA*** test for *Clonorchis sinensis* is based on the *cox1* gene (Rahman et al., 2017). This test can be used in peripheral laboratories based in endemic locations. The ***Gold Immunochromatography Assay (GICA)*** is an antibody detecting rapid test based on a yeast produced recombinant antigen that was not specified. The test sensitivity is lowest in light infections although it generally has good performance in light, moderate and heavy infections (Li et al., 2018). This test is simple to perform and can be used at community level.

3.3.3.4. Human paragonimiasis. The ***excretory-secretory lateral flow assay (ES-LFA)*** of *Paragonimiasis skrjabini* detects antibodies against excretory-secretory antigens. The reported sensitivity and specificity is 94.4% and 94.1%, respectively. Cross reactions with schistosomiasis and clonorchiasis positive samples were observed (Wang et al., 2014). The test is sufficiently simple but has a stage of serum dilution and cannot easily be used in a community setting but rather at clinic level in endemic areas.

3.3.4. Assessment of the diagnostic technology for commercialized point of care tests used in diagnosis of foodborne neglected zoonotic helminths using a standardized scorecard

Evaluation of diagnostic tests has largely been based on diagnostic performance, often reported as sensitivity and specificity, and other diagnostic accuracy measures such as, predictive values, likelihood ratios, odds ratios and area under the curve (Cohen et al., 2016; Eusebi, 2013). In some studies, operational characteristics of diagnostic tests are being included (Bocoum et al., 2015). Diagnostic tests for use in resource limited settings are additionally evaluated for operational performance in the absence of robust laboratory infrastructure. These tests which can be applied at the patient side in non-laboratory settings have been defined differently (Drain et al., 2014). A criteria, called the ASSURED was developed by WHO and applied to Human Immunodeficiency Virus (HIV) (Affordable (less than $500/machine, less $10/test), Sensitive (Acceptable analytical sensitivity: 500 HIV RNA copies/ml, 350 CD4 + T cells/μl), Specific, User-friendly (1–2 days training), Rapid (less than 30 min for diagnosis, less than 1.5 h for HIV load monitoring) and Robust, Equipment free or minimal and Deliverable to remote areas) (Wu and Zaman, 2012). This eight parameter criteria, which was specific to HIV tests has been expanded to include other essential parameters such as, features of consumables, quality and cost, enabling universal assessment of diagnostic tests in general and point of care tests specifically regardless of the disease they diagnose (Lehe et al., 2012). These expanded criteria use a score card with predefined weightings on each parameter. The results of the scorecard, given out of a 100 maximum scores can pass for percentage scores.

Table 3
Summary characteristics of rapid tests for foodborne trematodes infections in humans.

Disease	Fascioliasis	Fascioliasis	Fascioliasis	Opisthorchiasis	Opisthorchiasis	Opisthorchiasis	Clonorchiasis	Clonorchiasis	Paragonimiasis
Index Test	***IGS*-LAMP**	**rPCL1-sero fluke**	**ES-Dipstick**	***Mito*Ov-LAMP**	***ITS1*-LAMP**	***OVMS*-LAMP**	***Cox1*-LAMP**	**GICA**	**ES-LFA**
Reference test	PCR	Kato Katz, ELISA, Western blot, Hemaglutination assay	Microscopy, Indirect Hemaglutination, ELISA	Kato Katz	Microscopy after formal ethyl acetate concentration	ITS1-LAMP	Kato Katz, Real time PCR	Kato Katz, microscopy after water washing precipitation	ELISA
Diagnostic se %	–	100	100	–	100	–	97.1	94.96	94.4
Diagnostic sp %	–	100	96.7	–	65	–	92.5-100	85.23	94.1
Analytical se	10^{-5}ng	–	–	10^{-4}ng	10^{-3}ng	1 ng	100fg	–	–
Analytical sp (Other diseases/ parasites being tested to evaluate specificity)	*Opisthorchis viverrini, Clonorchis sinensis, Orientobilharzia turkestanicum, Schistosoma japonicum*	Fascioliasis, schistosomiasis. filariasis, hydatidosis, anisakiasis, toxocariasis, Chagas disease	Schistosomiasis, hydatidosis, toxoplasmosis, amoebasis	*C. sinensis, F. gigantica, F. hepatica, Fasciolopsis buski, Haplorchis pumilio, H. taichui*	*C. sinensis, Centrocestus. caninus, H. taichui*	*C. sinensis, C. caninus, H. taichui, Opisthorchis felineus, F. gigantica, Haplorchoodes sp*	*Metagonimus yokogawai, O. viverrini, F. gigantica, Spirometra erinacei, Diphyllobothrium latum, Ascaris lumbricoides, Ascaris suum, Necatus americanus, Trichuris trichiura, Cryptosporidium parvum, Entamoeba histolytica, Giardia lamblia, Escherichia coli*	Schistosomiasis, paragonimiasis, trichinellosis, ascariasis, trichuriasis, hookworm disease	Schistosomiasis, clonorchiasis
Cross reactions	No cross amplifications	No cross reactions	Schistosomiasis	No cross amplification	No cross amplification	No cross amplification	No cross amplification	Cross reactions recorded but not specified	Schistosomiasis, clonorchiasis and healthy controls
Study design	Experimental	Retrospective	Retrospective	Retrospective	Cross sectional, experimental	Cross sectional/ experimental	Retrospective	Cross sectional	Cross sectional
Population description	Fasciola DNA from various animals	Hospital referrals	Hospital referrals	–	Children from an endemic area	Parasite DNA from hamsters	Mixed residents of endemic community	Endemic population	Hospital referrals
Sample size	20	203	60	29	37	–	133	475	128
Positive samples	16		30	20	24	–	70	238	54
Negative samples	Each serial dilution had a negative control	12	5	1	13	Each serial dilution had a negative control	50	170	34
Heterologous infections	4	164	25	9	3	6	13	67	40
Test format	(LAMP)	Immuno-chromatography	Immuno-chromatography	LAMP	LAMP	LAMP	LAMP	Immuno-chromatography	Immuno-chromatography
Sample type and quantity	DNA from stool samples	Serum, whole blood 10 µL	Serum, 20 µL	DNA from 100 mg stool samples	DNA from 200 mg stool sample	DNA from 200 mg stool sample	DNA from 100 mg stool sample	Serum	Serum, 15µL
Time to results (Minutes)	45	10 serum, 20 whole blood	15	75	40	40	62	10	10
Reference	(Ai et al., 2010)	(Martínez-Sernández et al., 2011)	(Ali, 2012)	(Le et al., 2012)	(Arimatsu et al., 2012)	(Arimatsu et al., 2015)	(Rahman et al., 2017)	(Li et al., 2018)	(Wang et al., 2014)

Abbreviations: rpCL1- Recombinant pro-cathepsin L1, IGS- Intergenic spacer, ES- Excretory-secretory, Mito OV- Opisthorchis viverrini mitochondria, ITS1-Intergenic spacer 1, OVMS- Opisthorchis viverrini microsatellite, Cox 1- Cytochrome C oxidase subunit 1, GICA- Gold immuno-chromatography assay, LFA- Lateral flow assay, LAMP- Loop mediated isothermal amplification.

Table 4
Assessment of diagnostic technology of commercialized POC tests using the Scorecard: Percentage scores of the three echinococcosis commercialized tests.

Operational characteristics	Weighing (%)	Test score VIRapid	DIGFA	ADAMU-CE
POC features of equipment	29	20.30	23.20	21.27
POC features of consumables	8	5.87	2.67	3.73
Ease of use	34	30.60	24.65	26.35
Quality control	10	6.00	2.00	2.00
Cost	10	6.00	8.00	6.00
Total percentage	**91**	**68.77**	**60.52**	**59.35**

Where it has been used, test scores ranged between 71–100% (Lehe et al., 2012). The purpose of the score card is to rank and identify strengths and weaknesses of rapid tests based on their operational characteristics. In the reviewed manuscripts, the scorecard was applied to assess the operational suitability of three commercialized point of care tests for diagnosis of cystic echinococcosis. These tests are VIRapid (Vircell, Spain) (Delgado et al., 2010), DIGFA (UniBiotest, China)(Feng et al., 2010) and ADAMU-CE (ICST Corporation, Japan) (Santivañez et al., 2015) already discussed above. In this assessment, the last category of "distribution and service" which is country-specific was omitted so that the results can be generalized to any area, hence the total percentage weighting is 91% instead of 100% VIRapid performed best among the three diagnostic tests in this assessment (Table 4).

4. Discussion

In total, 25 rapid tests for the diagnosis of FNZH have been developed or further evaluated since 2010. Of the 25, there were eight RDT for *T. solium* infections, eight for echinococcosis and nine for FBT infections.

The majority of study designs (Fig. 2) were case-control studies in which subjects were not randomly selected. As such, the reported diagnostic performance was biased upwards (Whiting et al., 2013). However, when tests were subjected to evaluation in endemic populations, diagnostic performance was reduced due to spectrum of disease (Abdul et al., 2015). Given the varying disease prevalence that results from major interventions, it is important that these diagnostic tests are extensively evaluated to obtain full information on test performance in different epidemiological situations. Many RDTs that have been developed for FNZH have not undergone field performance evaluation. For LAMP tests, most were only evaluated on serial dilutions of DNA to obtain the analytical performance. To facilitate field performance evaluation, some NTDs such as *Schistosoma* spp., blinding trachoma, soil transmitted helminths and *T. solium* infections have diagnostic target product profiles produced to guide research and development of diagnostics (Donadeu et al., 2017; PATH, 2015). We have not come across target product profiles for diagnostic tests for Echinococcus and foodborne trematodes infections. Furthermore, beyond diagnostic accuracy evaluation, there is need to evaluate the clinic impact of rapid diagnostic tests on patient centered outcomes (Drain et al., 2014). The study quality as shown in Fig. 3 was generally similar in pattern. Few studies reported blinding and training of people involved in the diagnosis. Only 77% of the studies had a cross tabulation of results, nearly all nucleic acid detecting tests results were not cross-tabulated. The use of statistical uncertainties was limited to only 32% of the studies. The STARD provide guidelines on reporting of diagnostic studies (Cohen et al., 2016). This review should therefore be interpreted in the light of information from Figs. 2 and 3.

Operational characteristics of three commercialized tests for *E. granulosus* s.l., VIRapid, DIGFA and ADAMU CE have been evaluated using a standardized scorecard (Lehe et al., 2012). Based on our results, the VIRapid is the best suited operationally for use in low resource settings with a score of 68.77%. Coupled with the score on diagnostic evaluation (Baraquin et al., 2017), VIRapid would be the test of choice for CE in low resource settings. The evaluation on ADAMU CE was limited as the manufacturers did not provide further information required beyond what was on the product leaflet. Therefore, the assessment scores on heat stability of reagents and controls, shelf life and reagent, consumable and control costs were used at minimum scores. It is possible that, had the information been available, the overall scores could alter the sequence, especially with the DIGFA, which is just a few points above the ADAMU CE. The limitation with using the scorecard or the ASSURED criteria on diagnostic test is that some components of both criteria can only be determined in a marketed product. For example, affordability in ASSURED (less than $10) or cost in the scorecard is only known in commercialized products while in-development tests, these can only be estimated. Thus, in this study, cost was not part of the assessment for a test to meet the criteria. Furthermore, some thresholds are very species specific. For example, analytical sensitivity which has been described is specific to the human immunodeficiency virus (Wu and Zaman, 2012). This may explain why the two criteria have been used in assessment of commercial products only and not tests under development (Kelly et al., 2017; Lehe et al., 2012; Marks and Mabey, 2017). However, these two criteria stand as the closest reference description of POC tests that are available.

5. Conclusions

The results show that there is development of RDTs for FNZH. Most of the developed serological tests are based on the same antigens only changing test formats. The developed tests, despite their limitations are potentially capable of being used as tools in mapping and intervention monitoring especially when integrated with conventional tests. Further evaluation of most of these tests is needed to provide sufficient information on their applicability to endemic areas especially in low resource settings. There is also need to determine the value add of these tests in health outcomes of individuals. Further research is needed on the effect of test format on diagnostic performance.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.actatropica.2019.03.030.

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