Standards for design and reporting of test validation studies for detection of aquatic and terrestrial animal pathogens: are they needed?

Ian Gardner

Canada Excellence Research Chair:

Aquatic Epidemiology

UPEI
UNIVERSITY
of Prince Edward
ISLAND

Outline for presentation

- Test evaluation in animal health
  - Progress, challenges and weaknesses
- Design guidelines for infectious diseases of animals
  - World Organisation for Animal Health (OIE)
- Bayesian latent class methods for test evaluation



Outline for presentation

- Quality standards for reporting of test accuracy studies
  - Human health: STARD initiative
  - Animal health: STRADAS-paratuberculosis (first initiative)
- Expectations and predictions (next 10yr)

Progress

1990 to 1999

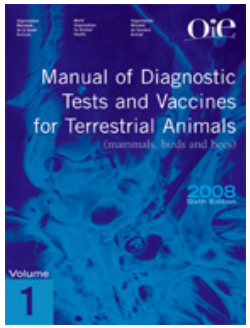
Recognition that diagnostic and analytic sensitivity and specificity not equivalent

Publications included Se/Sp estimates

First printing of OIE chapter on “Principles of test validation” (1996)

First latent class analysis (LCA) (1998)

Georgiadis *et al*. Field evaluation of sensitivity and specificity of a PCR for detection of *Nucleospora salmonis* in rainbow trout. J Aq. Anim. Health



2000 to 2012

Prev Vet Med special issue

Increased use of likelihood ratios, ROC analysis

Acceptance of utility of LCA because of imperfect reference standards.

LCA recognized by OIE (2008)

Manuscripts on design guidelines and reporting standards (2010/2011)

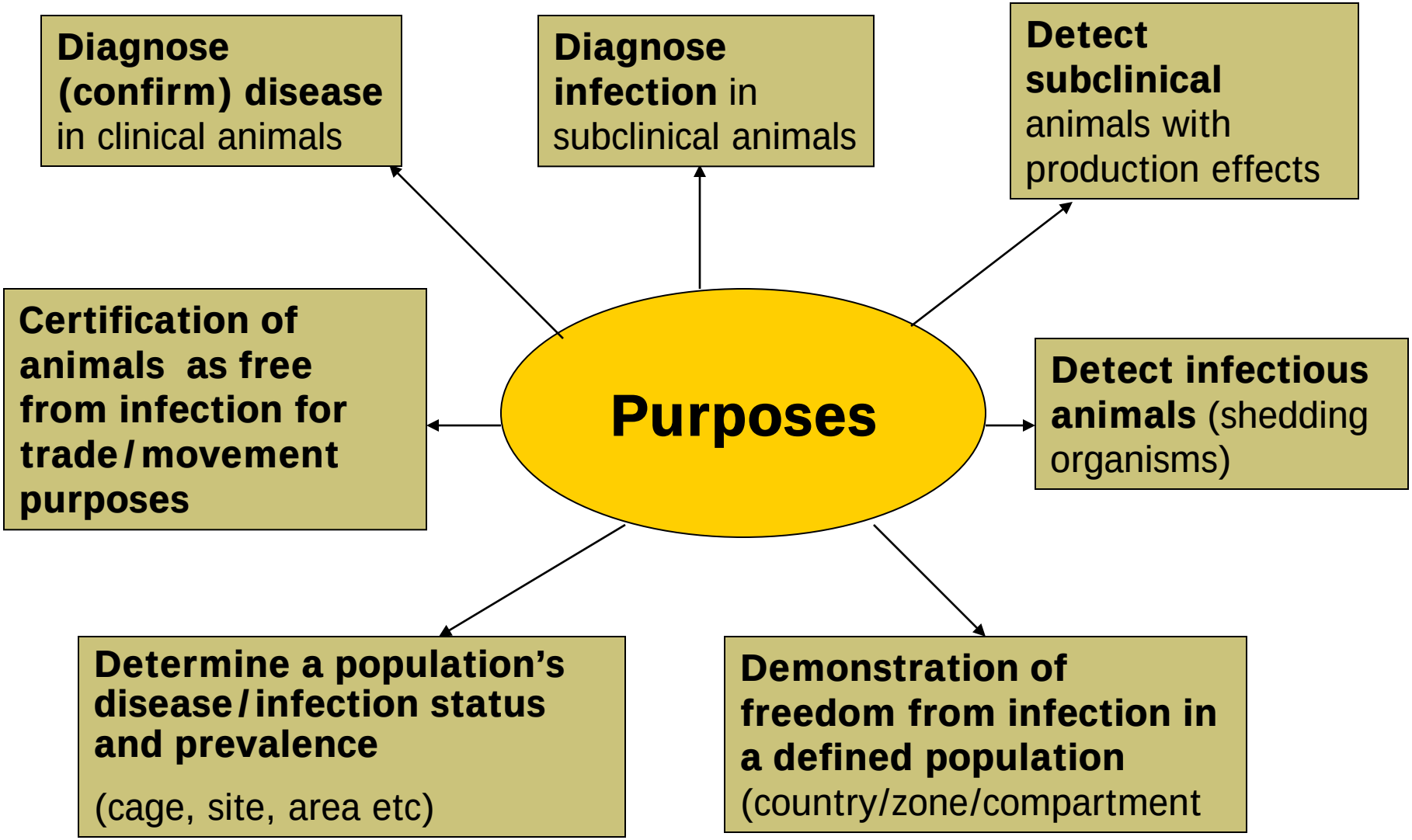
Challenges in animal health

- Testing purposes are more varied in animal populations than human populations
  - Multiple species, diverse matrices
  - Different epidemiological units
    - Individual
    - Aggregates

      (e.g. cage, site, area, zone)

- Limited resources (incl. funding)

Diagnostic testing purposes



Where are we now?....

- Design & reporting of studies are of variable quality
- Few financial evaluations of testing utility
  - Dorshorst et al. Decision analysis model for paratuberculosis control in commercial dairy herds. PVM 2006;75:92-122
- Only 2 published meta-analyses/systematic reviews
  - Bovine tuberculosis skin tests
  - Culture and PCR for *Salmonella* spp. in swine
- Few studies on prognostic value of tests relative to important health outcomes
- Latent class analysis methods sometimes lack rigorous implementation

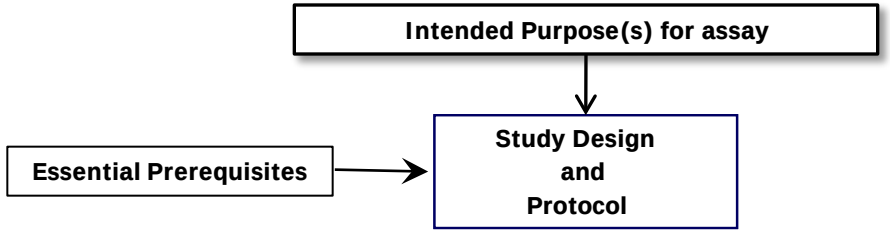
World Organisation for Animal Health (OIE) guidelines

- Original focus – trade/international movement of economically important infectious diseases
  - 116 currently listed
- New focus – “One Health”
  - Increased interest in wildlife diseases and validation of tests for wildlife spp.
- Two topics
  - OIE Manual chapter & Registry of Certified Tests

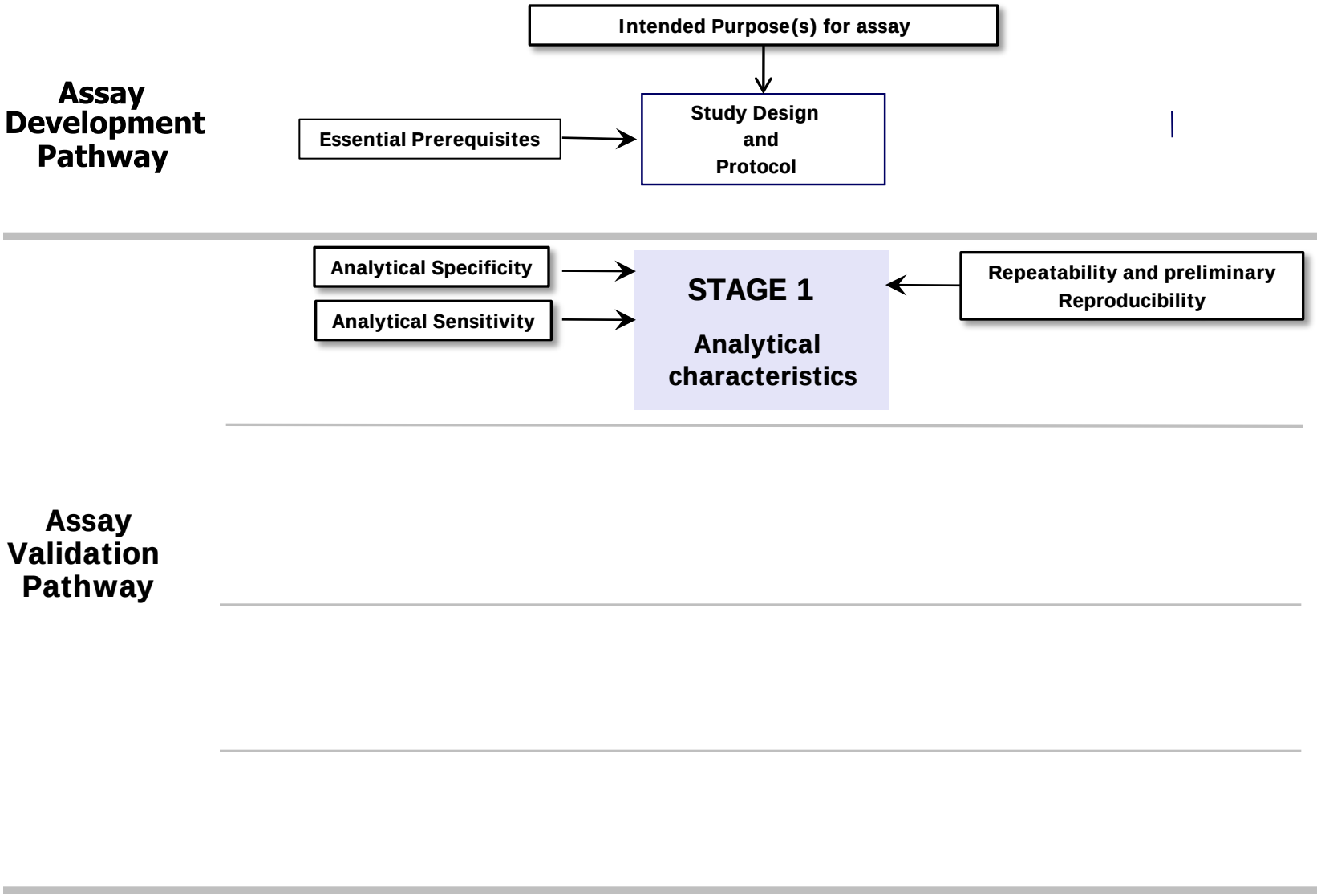
OIE chapter

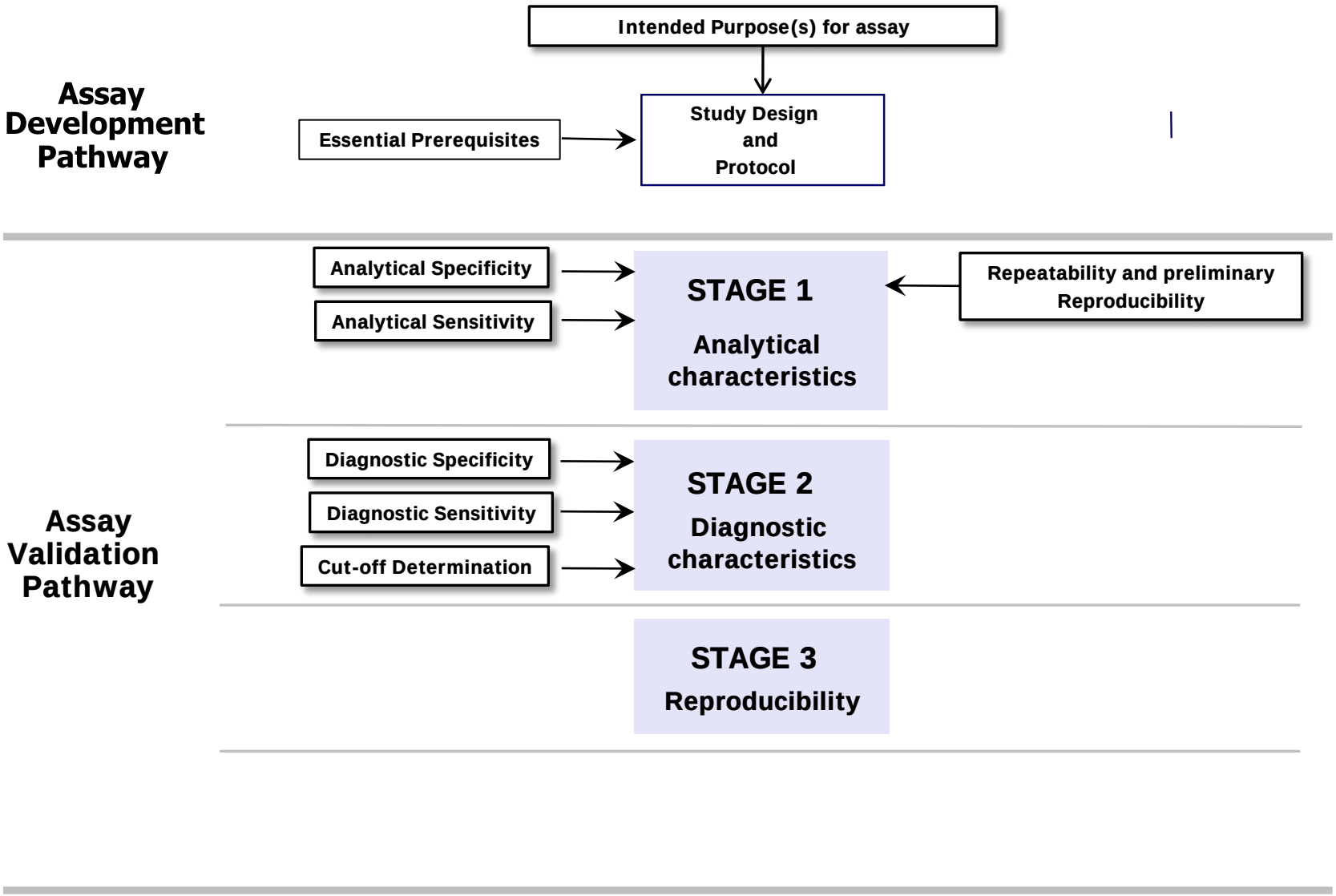
- Principles of Validation of Diagnostic Tests - May 2013 (for member country vote)
  - Chapters on serology and PCR merged
    - Focus on “fitness for purpose”
  - Annexes
    - Serologic tests; nucleic acid detection; TSE detection; statistical analysis methods; quality assurance; reference samples

Assay Development Pathway



Assay Validation Pathway


Assay Development Pathway
Intended Purpose(s) for assay
Essential Prerequisites
Study Design and Protocol
Assay Validation Pathway
Analytical Specificity
Analytical Sensitivity
STAGE 1
Analytical characteristics
Repeatability and preliminary Reproducibility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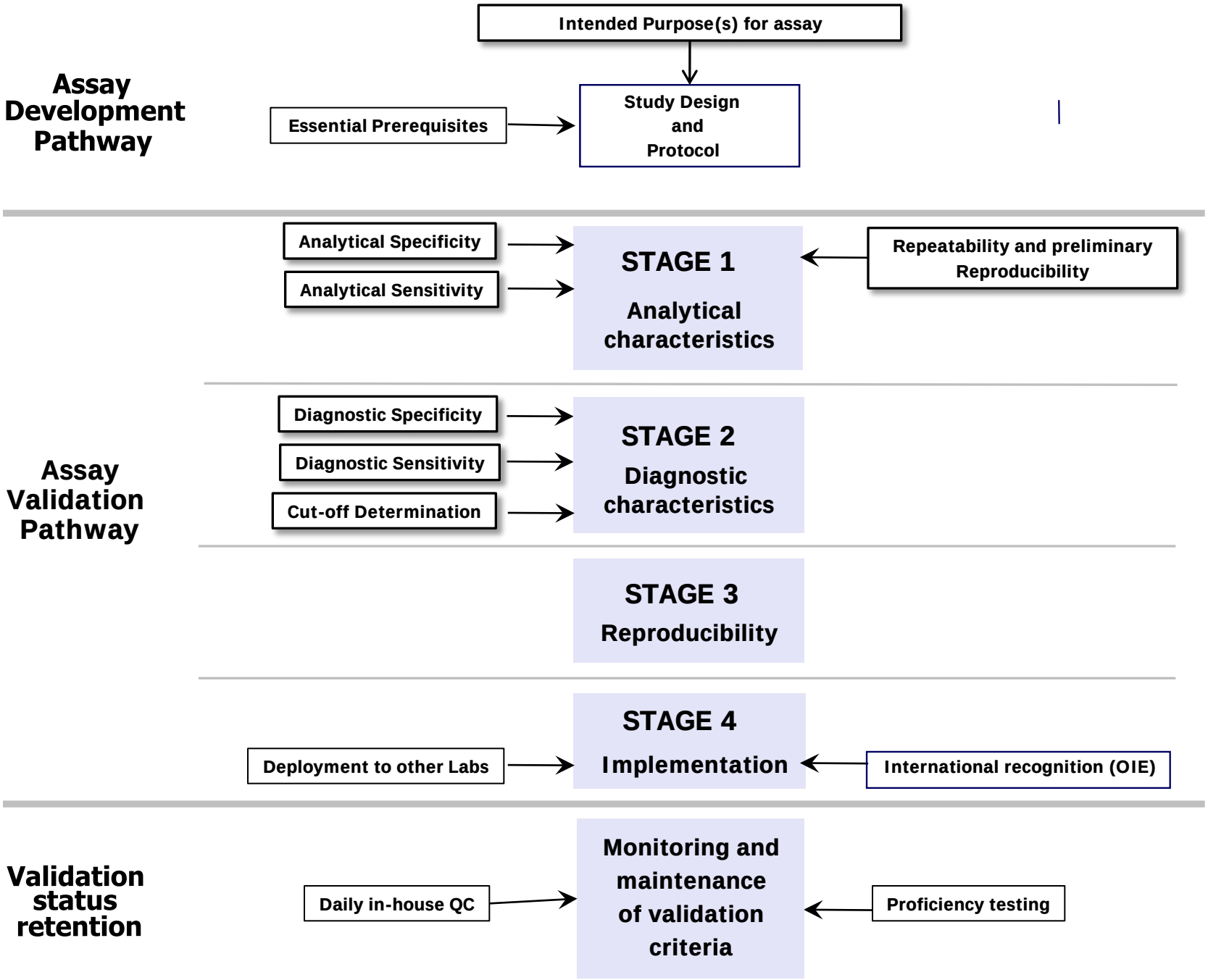
Repeatability and preliminary Reproducibility
Diagnostic Specificity
Diagnostic Sensitivity
Cut-off Determination
STAGE 2
Diagnostic characteristics
STAGE 3
Reproducibility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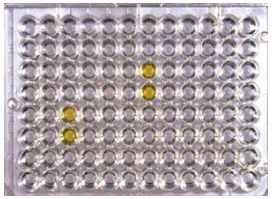
Diagnostic characteristics
STAGE 3
Reproducibility
STAGE 4
Implementation
Deployment to other Labs
International recognition (OIE)
Validation status retention
Daily in-house QC
Monitoring and maintenance of validation criteria
Proficiency testing

OIE registry of tests

- Certified as “fit for purpose”
- Main target is companies supplying kits
  - ELISAs



  - PCR
  - Euro 8000 for review of dossier

www.oie.int/en/our-scientific-expertise/certification-of-diagnostic-tests/the-register-of-diagnostic-tests/

Register of diagnostic kits certified by the OIE as validated as fit for purpose

'Fit for purpose' means that the kit has to be validated to such a level to show that the kit's results can be interpreted to have a defined meaning in terms of diagnosis or another biological property being examined.

Bovine spongiform encephalopathy	Prionics AG - Check Western	Prionics AG	info@prionics.com	Western Blot	see Resolution No XXVII adopted in May 2008 by the World Assembly of the OIE Delegates	May 2008 Registration Number: 20080102	AS Prionics AG-Check WESTERN	User's manual
Transmissible Spongiform Encephalopathies	TeSeE™ Western Blot	Bio-Rad	tse@bio-rad.com	Western Blot	see Resolution No XXVI adopted in May 2009 by the World Assembly of the OIE Delegates	May 2009 Registration Number: 20090105	AS TeSeE WB	User's manual
Salmonellosis	Check&Trace Salmonella	Check-Points B.V.	serovar@check-points.com for technical questions info@check-points.com for general questions	Multiplex LDR PCR reaction followed by detection on a diagnostic micro array	see Resolution No 24 adopted in May 2011 by the World Assembly of the OIE Delegates	May 2011 Registration Number: 20110106	AS CTS	User's manual
Bovine tuberculosis	Mycobacterium bovis Antibody Test Kit	IDEXX Laboratories	lpdtechservices.com	Indirect ELISA	see Resolution No 24 adopted in May 2012 by	May 2012 Registration Number: 20120107	AS MBAT	User's manual

Technological developments

- PCR is replacing bacterial, virus, and parasite isolation for routing diagnostic use
- Challenges in PCR validation
  - Never show PCR technology is more accurate than imperfect reference test (e.g. virus isolation) by traditional statistical methods
  - Latent class analysis is a solution when reference test in imperfect

MAJOR ARTICLE

Clinical Infectious Diseases 2012;55(3):322–31

Fool's Gold: Why Imperfect Reference Tests Are Undermining the Evaluation of Novel Diagnostics: A Reevaluation of 5 Diagnostic Tests for Leptospirosis

Direk Limmathurotsakul,[1,2] Elizabeth L. Turner,[7] Vanaporn Wuthiekanun,[2] Janjira Thaipadungpanit,[2] Yupin Suputtamongkol,[5] Wirongrong Chierakul,[2,3] Lee D. Smythe,[6] Nicholas P. J. Day,[2,8] Ben Cooper,[2] and Sharon J. Peacock[2,4,9]

[1]Department of Tropical Hygiene, [2]Mahidol-Oxford Tropical Medicine Research Unit; [3]Department of Clinical Tropical Medicine, [4]Department of Microbiology and Immunology, Faculty of Tropical Medicine, [5]Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [6]WHO/FAO/OIE Collaborating Centre for Reference and Research on Leptospirosis, Centre for Public Health Sciences, Queensland Health Scientific Services, Brisbane, Australia; [7]Department of Medical Statistics, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, [8]Centre for Clinical Vaccinology and Tropical Medicine, Nuffield Department of Clinical Medicine, Churchill Hospital, University of Oxford, and [9]Department of Medicine, Cambridge University, Addenbrooke's Hospital, United Kingdom

Background. We observed that some patients with clinical leptospirosis supported by positive results of rapid tests were negative for leptospirosis on the basis of our diagnostic gold standard, which involves isolation of *Leptospira* species from blood culture and/or a positive result of a microscopic agglutination test (MAT). We hypothesized that our reference standard was imperfect and used statistical modeling to investigate this hypothesis.

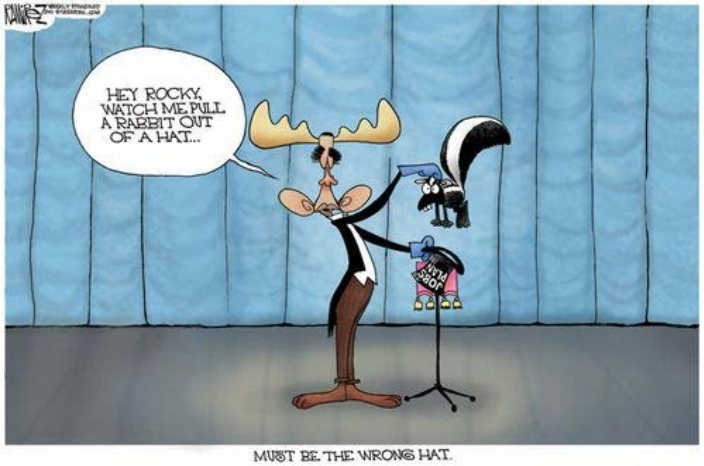
Latent class analysis

Wes Johnson

"Like pulling a rabbit out of a hat"

Nils Toft

"Like pulling something out of a hat and calling it a rabbit"



Latent class analysis: imperfect reference test

- Bacterial culture typically used as the reference test in food-borne pathogen test evaluation studies -- poor sensitivity
  - Many food matrices and sample tissues (feces) have high bacterial loads and low numbers of the target organism
  - Limited specimen sizes are tested

Example: *invA*-gene-based PCR for Salmonella in pigs

Mainar–Jaime et al.
Zoonoses and Public Health
Z008; 55:112-118

	Culture +	Culture -
PCR +	28	39
PCR -	1	135
	29	174

Problem: PCR can never be more sensitive than culture, if culture is reference test

Example: *invA*-gene-based PCR for Salmonella in pigs

- Accuracy of PCR compared with culture
  - Relative sensitivity = 28/29 = 0.966

    Relative specificity = 135/174 = 0.776

    or
  - Kappa, a measure of relative agreement beyond chance = 0.480 (poor)

- Neither of these approaches very useful!

Latent class analysis

- Assume neither PCR nor culture is perfect
  - True infection status is unobserved (“latent”)
- To make problem solvable mathematically
  - Add at least 1 more test, or
  - Add at least a second population or divide the original data by herd size

    (approach used here)

Example: *invA*-gene-based PCR for Salmonella in pigs

Data for all pigs

	Culture +	Culture -
PCR +	28	39
PCR -	1	135
	29	174

Example: *invA*-gene-based PCR for Salmonella in pigs

Small herds (n=96)

		Culture +	Culture -
PCR	+	6	11
	-	0	79
		6	90

Large herds (n=107)

		Culture +	Culture -
PCR	+	22	28
	-	1	56
		23	84

Example: *invA*-gene-based PCR for Salmonella in pigs

- Model assumptions (2 tests, 2 populations)
  - Constant sensitivity and specificity
    - Collection, handling and testing scheme for samples from 2 populations was identical
  - Independence of test errors, conditional on true infection status
  - Different prevalences in the 2 populations

Example: *invA*-gene-based PCR for Salmonella in pigs

- **Bayesian analysis**
  - Use prior information about the test accuracy, if available, from published studies or via expert opinion
  - Most likely scenario would be estimates for culture as the reference test
    - Perfect or almost perfect specificity

    (99.9% or about 1 false-positive in 1000 samples)

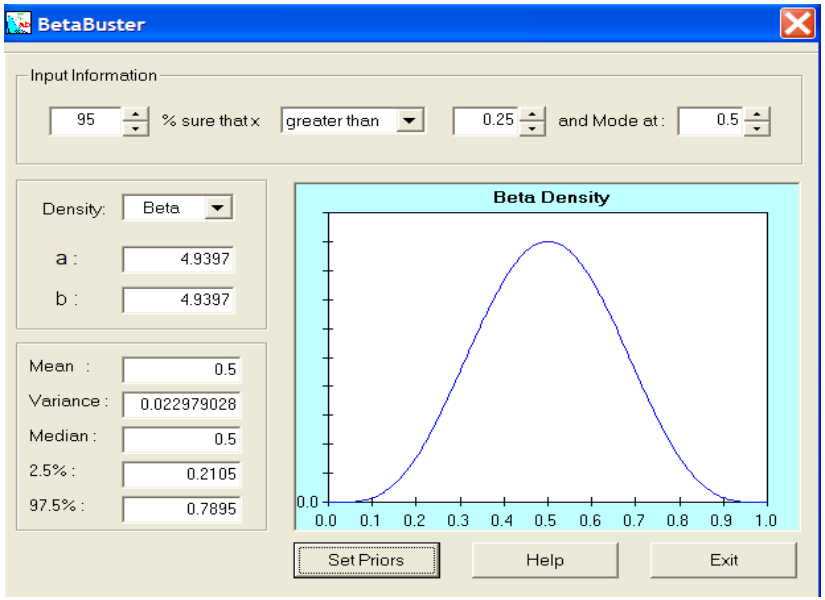
Prior distributions

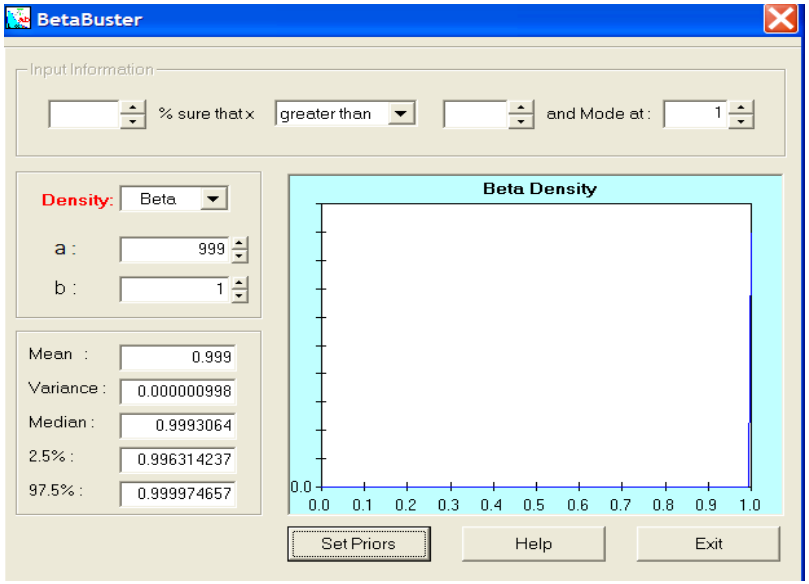
- Published studies (comparable design)
- Elicitation of prior from expert
  - Most plausible value (mode)
  - Value that expert is 95% sure that the value exceeds (or is less than)
  - Estimate appropriate beta (a,b) distribution using BetaBuster software

www.epi.ucdavis.edu/diagnostictests/

Examples of priors

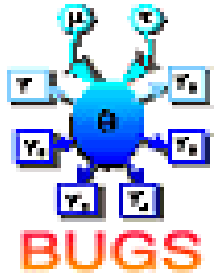
- Weakly informative
  - Beta (4.9, 4.9) for Sensitivity of culture
- Highly informative
  - Beta (999,1) for Specificity of culture





- Non-informative: beta (1,1); similar to maximum likelihood

Bayesian analysis



- WinBUGS software for implementation
  - Uses Markov chain Monte Carlo (MCMC) methods to approximate the posterior distributions
  - Software available free at:

    www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml
- Generates point estimates (median, mean) and probability intervals for all parameters
- Sample code for test evaluation at:

  www.epi.ucdavis.edu/diagnostictests/

WinBUGS results

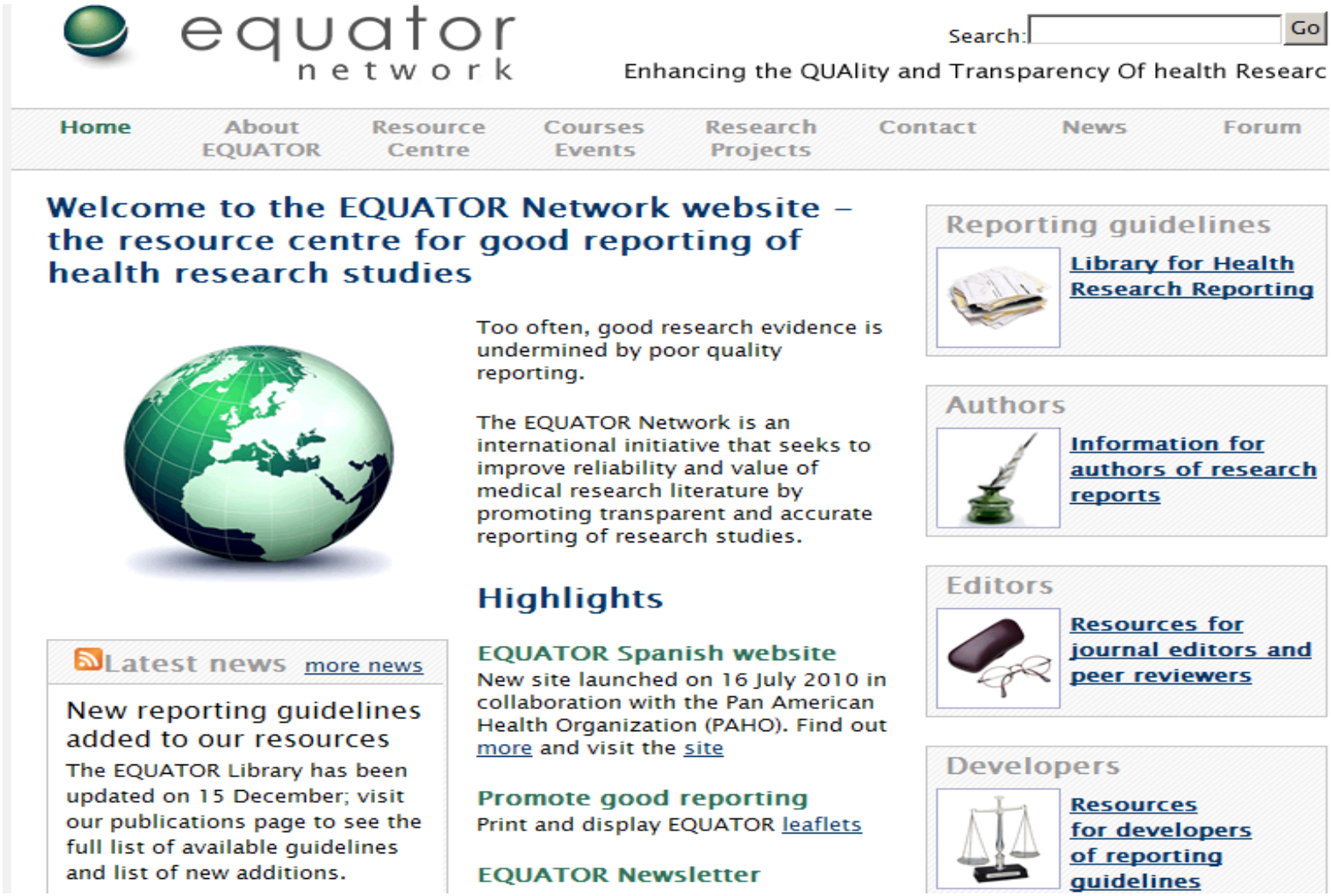
Node statistics

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
SeCult	0.4917	0.0921	7.163E-4	0.3355	0.4831	0.6968	501	49500
SePCR	0.9353	0.04475	2.954E-4	0.8242	0.9449	0.9932	501	49500
SpCult	0.9991	9.353E-4	7.752E-6	0.9965	0.9994	1.0	501	49500
SpPCR	0.9245	0.04659	3.939E-4	0.8215	0.9293	0.9952	501	49500
pi1	0.1348	0.0478	3.304E-4	0.05365	0.1312	0.2364	501	49500
pi2	0.4462	0.0668	4.958E-4	0.3079	0.4484	0.5711	501	49500

Bayesian: Se of PCR = 94.5% vs. Se of culture = 48.3%

Traditional: Se of PCR = 96.6% vs. Se of culture = 100% (gold standard)

Reporting standards for health research



www.equator-network.org

Reporting standards in health research

equator network

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Enhancing the QUAlity and Transparency Of health Research

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Resource Centre

- **Library for health research reporting**
  - Reporting Guidelines
  - Reporting guidelines under development
  - Reporting guidelines in other research fields
  - Guidance on scientific writing
  - Guidance developed by editorial groups
  - Medical writers – additional resources

Library for health research reporting

The EQUATOR Network library currently contains:

- An introduction to reporting guidelines
- Comprehensive lists of the available reporting guidelines, listed by study type:
  - Experimental studies
  - Observational studies
  - Diagnostic accuracy studies
  - Reliability and agreement studies
  - Systematic reviews
  - Qualitative research
  - Economic evaluations
  - Quality improvement studies
  - Other reporting guidelines
  - Reporting data
  - Sections of research reports
  - Specific conditions or procedures.
- Reporting guidelines under development
- Reporting guidelines in other research fields

Download the most frequently–used reporting guidelines:

- CONSORT checklist
- CONSORT flowchart
- CONSORT extensions
- STARD checklist & flowchart
- STROBE checklists
- PRISMA checklist
- PRISMA flow diagram

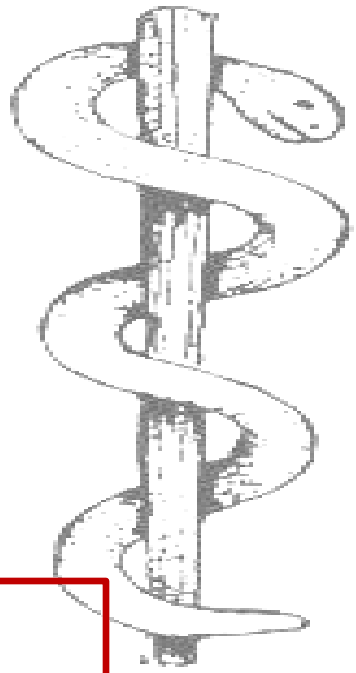
www.equator-network.org

Human diagnostics

- **STA**ndards for **R**eporting of **D**iagnostic Accuracy (**STARD**) steering committee statement /checklist (January 2003)

  www.stard-statement.org

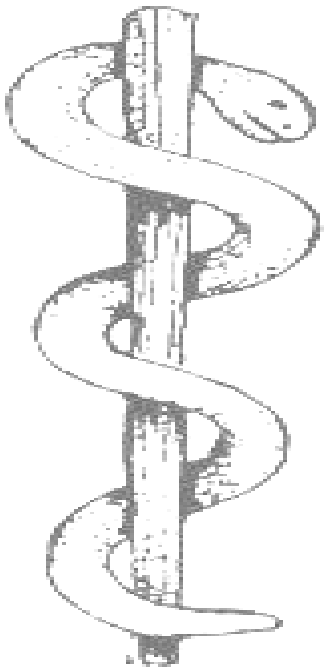
- Goal is complete and accurate reporting of test evaluation studies



- avoid use of “worthless” tests that don’t improve health outcomes

Human diagnostics

- **STARD** is a set of guidelines (25 items) for transparent and complete reporting
- **STARD** is not prescriptive about how a study is designed or analyzed
  - Design depends on test purpose
  - Different designs and data analysis methods might be appropriate for the same purpose



STARD endorsement

- More than 200 biomedical journals referenced STARD in their Instructions to Authors (April 2008)
- Four veterinary journals but nothing in aquatics
  - Veterinary Clinical Pathology (2007 editorial)
  - Preventive Veterinary Medicine (2009)
  - BMC Veterinary Research
  - Acta Veterinaria Scandinavica

Rationale for quality standards

- Lack of clarity and transparency of reporting associated with overly optimistic estimates
  - Sensitivity & specificity in test evaluation studies
- Good reporting
  - Reveals strengths and weaknesses of a study
  - Reduces the risk of spurious findings not standing up to replication
- Guidelines in these initiatives helpful for:
  - Peer-reviewers and editors in their evaluation of manuscripts; authors in planning studies

STARD checklist for reporting of studies of diagnostic accuracy

Section and Topic	Item #	
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.
METHODS		
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?

Has STARD made a difference to reporting quality?

- Minimally, uptake and utilization limited
  - Not an issue of what is in STARD
  - Factors influencing journal editor and author uptake need to be determined
  - Should end-users/readers be more outspoken about the lack of completeness in reporting?
- Example
  - TB, HIV and malaria - PlosOne 2009; 4: e7753

Diagnostic challenges in test evaluation studies of paraTB (*Mycobacterium paratuberculosis*):

- Protracted incubation period with latent infection
- Unpredictable disease progression
- Infection with different strains
- Low paraTB organism loads in tissues and feces of many animals
- Intermittent shedding of organism in feces
- Diverse testing purposes and specimen types

Diagnostic Zealot

Claim:

"My test uses the latest technology and has to be better than your test. Trust me"

Response:

"Show me the data. I suggest a **blinded comparison** of the 2 tests and a **cost-effective analysis** for a **designated purpose"**

Paratuberculosis (*M. paratuberculosis*): quality of published manuscripts

"There is a profound lack of reliable test evaluations, and future assessments should be conducted more stringently to allow appropriate interpretation and comparison across populations"

Vet Microbiol 2008:129:217-235

ParaTB: manuscript quality

- Important test evaluation components identified by Nielsen and Toft – 94 studies
  - Data must be observational (non-experimental)
  - Study population should be representative of the target population
  - Target condition (affected, infectious, infected etc.) should reflect the purpose of the test and be evaluated for both sensitivity and specificity
  - Calculated sample size should reflect the purpose of the test evaluation

Veterinary Microbiology 150 (2011) 115–125

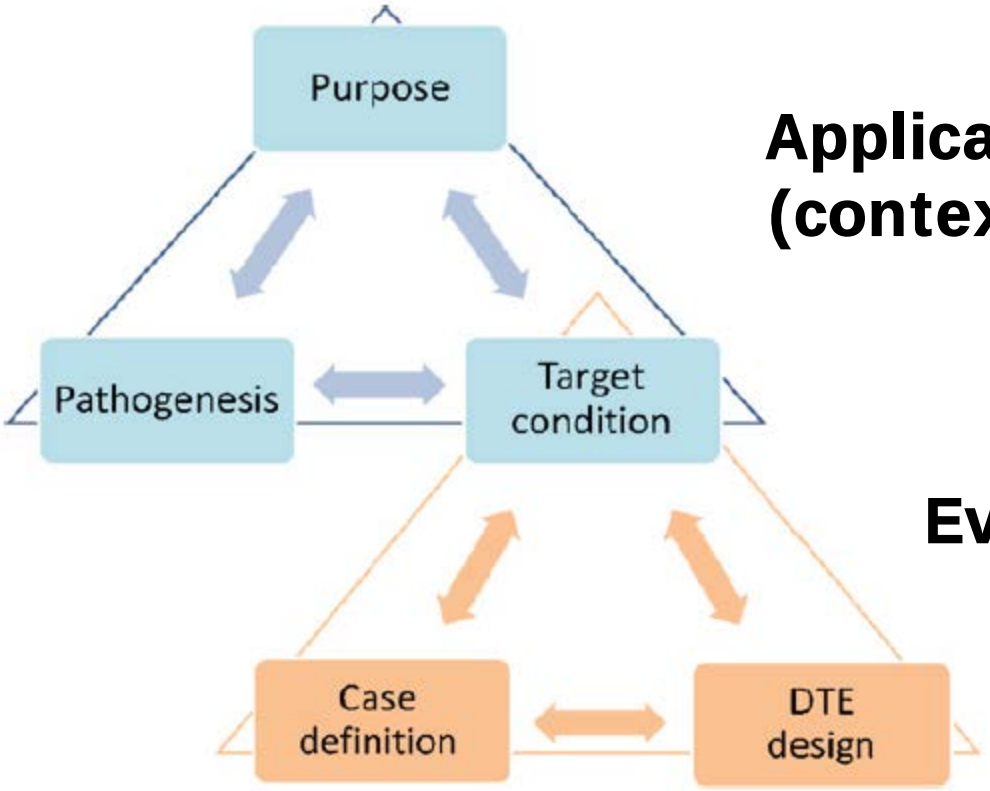
Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Structured approach to design of diagnostic test evaluation studies for chronic progressive infections in animals

Søren Saxmose Nielsen [a,b,*], Nils Toft [a,b], Ian Andrew Gardner [a,b]



Application (context) triad

Evaluation triad

Preventive Veterinary Medicine xxx (2011) xxx–xxx

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Consensus-based reporting standards for diagnostic test accuracy studies for paratuberculosis in ruminants

Ian A. Gardner[a,*], Søren S. Nielsen[b], Richard J. Whittington[c], Michael T. Collins[d], Douwe Bakker[e], Beth Harris[f], Srinand Sreevatsan[g], Jason E. Lombard[h], Raymond Sweeney[i], David R. Smith[j], Jerrie Gavalchin[k], Shigetoshi Eda[l]

[a] *Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, CA 95616, USA*
[b] *Department of Large Animal Sciences, Faculty of Life Sciences, University of Copenhagen, Grønnegardsvej 8, DK-1870 Frederiksberg C, Denmark*
[c] *Faculty of Veterinary Science, The University of Sydney, 425 Werombi Road, Camden 2570, NSW, Australia*
[d] *Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI 53703-1102, USA*

Table 1
Checklist of items for reporting of diagnostic test accuracy studies for paratuberculosis in ruminants based on the STARD checklist (statement.org).

Section and topic	Item	Description of item
Title/abstract/keywords	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').
Introduction	2	State the research question or study aims such as estimation of diagnostic accuracy or comparison of accuracy between tests ***in a specified matrix (specimen type) for a defined purpose at the animal or herd level***
Materials and Methods		
Animals and herds	3	***Describe study sampling frame: Describe the source population*** and inclusion and exclusion criteria, setting and locations where data were collected ***for all relevant levels of the study sample (animals and herds)***
	4	***Describe selection of animals and herds: Describe sample selection methods (random, convenience, etc.) within each level of the sampling hierarchy (e.g. regions, farms, barns, cows) including exclusion criteria and number of study animals and herds.***
	5	***Describe sampling protocol: Describe the collection, specimen size, transportation, handling and storage of specimens prior to the performance of the test under evaluation (TUE) and the reference standard.***
	6	Describe ***study design***: Was data collection planned before the TUE and reference standard were performed (prospective study) or after (retrospective study)?

Test methods	7	Describe the reference standard and its rationale.
	8	Describe technical specifications of materials and methods involved including how and when measurements were taken, and/or cite references for TUE and reference standards. ***Specify quality control samples for TUE and reference standard and specimen/analytical unit size of tested samples.***
	9	Describe the ***outcome measure and rationale for the cutoffs*** and/or categories of the results of the TUE and reference standard.
	10	Describe the ***name, location, and qualifications of the laboratory***, including the number, training and expertise of persons executing the TUE and reference standard.
	11	Describe whether or not the readers of the TUE and reference standard were blind (masked) to the results of the other test and describe ***any individual or herd-level information available to the readers.***
Statistical methods	12	Describe methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).
	13	Describe methods for calculating test ***repeatability and*** reproducibility, if done.
Results		
Animals and herds	14	Report when study was done, including beginning and end dates of recruitment
	15	***Report demographic and other biologically relevant characteristics of the study sample at the individual (e.g. age, sex, breed, and risk factors) and at the herd levels (e.g. production system).***
	16	Report the ***number of animals and herds*** satisfying the criteria for inclusion that did or did not undergo the TUE and/or the reference standard; describe ***why animals and herds*** failed to receive either test.

Test results	17	Report time interval ***between collection of samples for the TUE and the reference standard, and interventions*** administered between.
	18	Report distribution of severity of disease or stage of infection (define criteria), ***and other relevant diagnoses or treatments in animals in the study sample.***
	19	Report a cross tabulation of the results of the TUE (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.
	20	Report any adverse events from performing the TUE or the reference standard.
Estimates	21	Report estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).
	22	Report how indeterminate results, missing responses and outlier values ***of the TUE and the reference standard*** were handled. If additional testing of animals and herds is done to resolve discrepant results, then describe the rationale and approach (a flow diagram is strongly recommended).
	23	Report estimates of variability of diagnostic accuracy between ***relevant subpopulations***, readers, ***or testing sites***, if done.
	24	Report estimates of test ***repeatability and*** reproducibility, if done.
Discussion	25	***Discuss the utility of the TUE in various settings (clinical, research, surveillance*** **etc.)** ***in the context of the currently available tests.***

Item:2 State the research question or study aims such as estimation of diagnostic accuracy or comparison of accuracy between tests in a specified matrix (specimen type) for a defined purpose at the animal or herd level.

Example

The aim of this study was to develop and evaluate a method for culturing of fecal samples pooled from a number of sheep in order to provide an economical test for *M. avium* subsp. *paratuberculosis* in flocks. Specific aims were to determine an acceptable rate of pooling of fecal samples, to compare the sensitivities of pooled fecal culture and an AGID [agar gel immunodiffusion] test, to evaluate the practicality of sample collection, and to develop recommendations for sampling rates for confirmation of *M. avium* subsp. *paratuberculosis* infection in flocks (Whittington et al., 2000).

Explanation

A clearly defined research objective relative to the TUE enables the reader to determine the validity of the test evaluation study in the context of the purpose of testing. The OIE endorses the concept of "fitness for purpose" in validation of diagnostic tests and lists 6 purposes: (1)

Expectations

- **Great emphasis on design and reporting quality** of primary test evaluation studies
  - More “head-to-head comparisons” (benchmarking) of competing technologies on the same sample sets
  - Greater stringency in journal review process
- **More transparency when tests are used about stage / rigor of validation**
  - e.g. “This test has been validated to stage 1 of OIE pathway for the purposes of certifying freedom from infection. No estimates of diagnostic sensitivity and specificity are available for this purpose”

Expectations

- **STARD will be adapted to other important animal infectious diseases**
  - Chronic diseases e.g. TSEs, bovine TB
  - Food-borne pathogens
- **Standards for reporting of latent class analyses will be developed for general guidance**
  - Ruminant paratuberculosis ?
- **More studies of cost-effectiveness of testing to producers & regulators (rather than estimation of sensitivity and specificity alone)**

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Questions?