Locksley Messam
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Diagnostic test evaluation with Bayesian latent class models

UCD DUBLIN

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EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

COST is supported by the EU Framework Programme Horizon 2020

HARMONY
Novel tools for test evaluation and disease prevalence estimation

1

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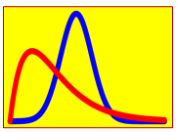
Diagnostic Tests



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HARMONY
Novel tools for test evaluation and disease prevalence estimation

	D+	D-
T+	TP	FP
T-	FN	FN

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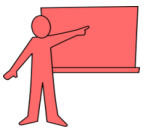
2



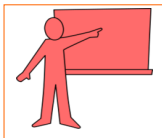
Epictetus (AD 55 – 135)

"**Appearances to the mind are of four kinds:**

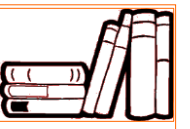
- Things either are what they appear to be; **TP**
- or they neither are, nor appear to be; **TN**
- or they are, and do not appear to be; **FN**
- or they are not, and yet appear to be. **FP**

Rightly to aim in all these cases is the wise man's task."

3



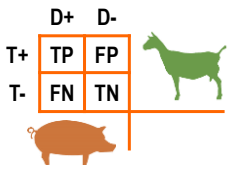
Topics



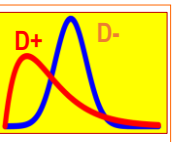
- Diagnostic tests (Definition, Types, Uses)
- Diagnostic Test Characteristics
- Applications of Diagnostic Tests

	D+	D-
T+	TP	FP
T-	FN	FN

4

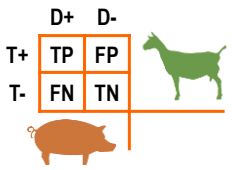


Diagnostic Tests

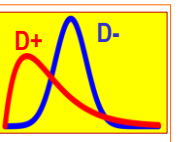


"Any device or process designed to detect a sign, substance, tissue change or response."

5



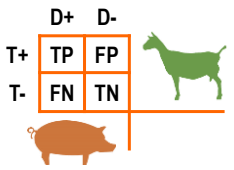
Diagnostic Tests



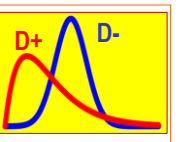
"…sign, substance, tissue change or response."

- Not necessarily disease
- Outcome of interest: Pregnancy checks via palpations, X-rays, Ultrasounds,….., Confounders too!!!

6



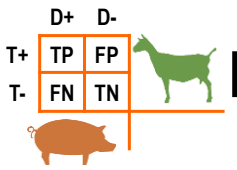
Diagnostic Tests



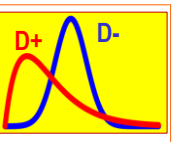
- **Dichotomous:** Fever, bacteria present?, Broken limb – Yes or No.
- **Ordinal:** Serologic Titres (1:50, 1:250, 1:500), lameness severity (1 - 5), Body condition score, Pain level (1-10)
- **Continuous scale:** WBC count, Temperature

Ordinal & continuous ⇒ Dichotomous *(i.e., +/- at given cut off).*

7

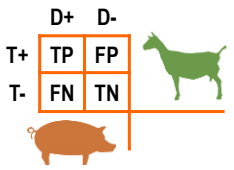


Diagnostic Tests: Uses

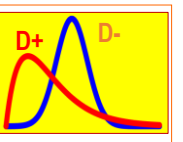


- **Detect (screen) or confirm** disease, infection, infectiousnes (individual or group)
  - Isolation and eradication (test and removal of reactors – Vet. Med.)
- **Institute preventive measures**: Human (Covid-19) & Vet. Med.
- **Monitor vaccination status:** Rabies, Tetanus

8



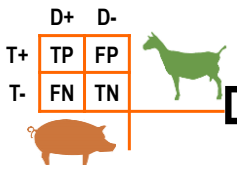
Diagnostic Tests: Gold Standard



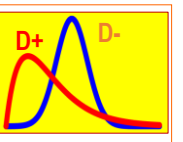
"A diagnostic method (or combination of methods) which determines without error, whether or not the organism has the condition (outcome).."

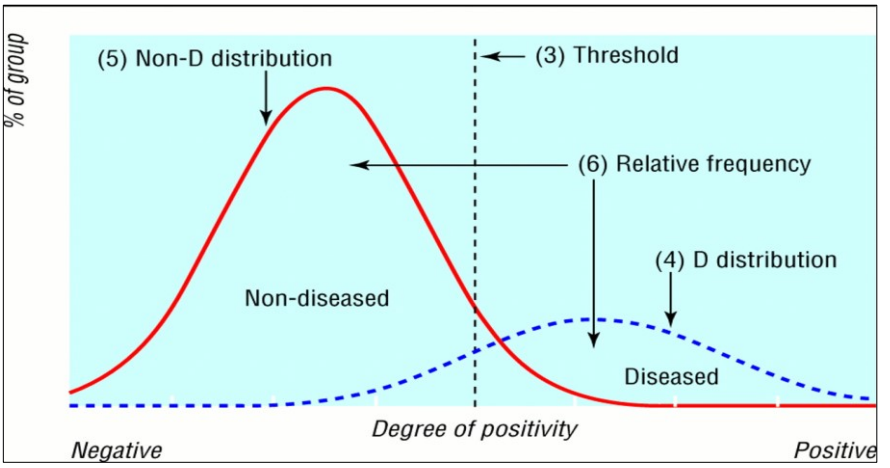
- Many diseases = no gold standard or not practical (costly, invasive)
- Vet. Med. - Few gold standards (if any)

9



Diagnostic Tests: Diseased and Non-Diseased





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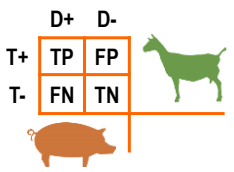
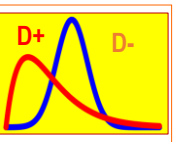
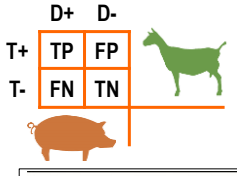


Diagnostic Tests

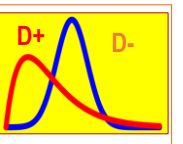


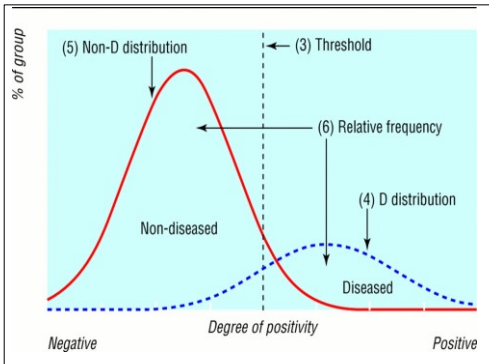
	D+	D-	
T +	Diseased and test Positive **(TP)**	Not diseased but test positive **(FP)**	TP + FP
T -	Diseased but test negative **(FN)**	Not diseased and test negative **(TN)**	TN +FN
			TP + FP + TN +FN

11



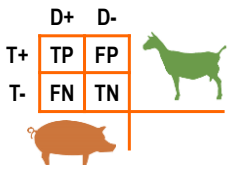
Diagnostic Tests



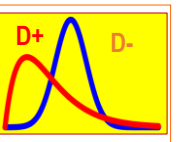


	D+	D-	
T +	TP	FP	TP + FP
T -	FN	TN	TN +FN
	TP+FN	FP+TN	TP+FP+TN+FN

12

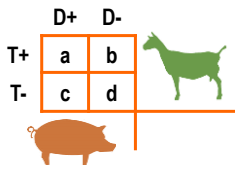


Diagnostic Tests: Gold Standard

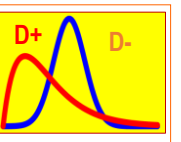


	D+	D-	
T +	Diseased and test Positive **(TP)**	**FP = 0**	**TP + FP**
T -	**FN = 0**	Not diseased and test negative **(TN)**	**TN +FN**
	TP + FN	**FP + TN**	**TP + FP + TN +FN**

13



Diagnostic Tests (Characteristics)

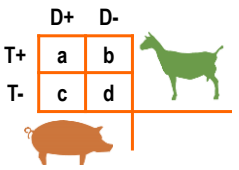


Sensitivity:

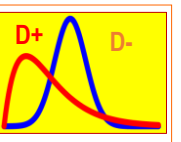
- Probability that randomly chosen diseased individual will test positive = P (T+|D+)
- Proportion of diseased that test positive
- Range 0 - 1 (0 – 100%)
- Gold Standard: Se = 100

$$Se = \frac{\text{Number of diseased individuals testing positive}}{\text{Total number of diseased individuals}} = \frac{a}{a + c} = \frac{TP}{TP + FN}$$

14



Diagnostic Tests (Characteristics)

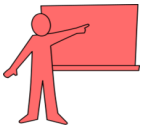


Specificity:

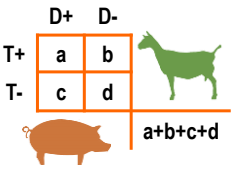
- Probability that randomly chosen non-diseased individual will test negative = P(T-|D-)
- Proportion of non-diseased that test negative
- Range: 0 - 1 (0 - 100%)
- Gold Standard: Sp = 100%

$$Sp = \frac{\text{Number of non-diseased individuals testing negative}}{\text{Total number of non-diseased individuals}} = \frac{d}{b+d} = \frac{TN}{TN+FP}$$

15



Diagnostic Tests: (Factors affecting Se and Sp)

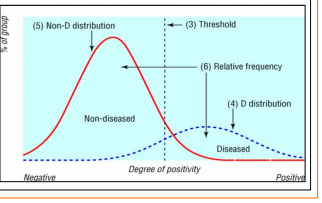


$$Se = \frac{a}{a+c}$$

- **Source population (disease stage)** – e.g. TB lower sensitivity - *early, late stages, after calving*
- **Choice of cut-off (continuous tests)** – Se decreases with increase in cut-off (vice-versa)
- **Prevalence** – complex - distribution of biological factors related to infection also related to prevalence.

$$Sp = \frac{d}{b+d}$$

- **Cross-reacting agents** (Serologic tests) – Similar Antibodies (*E. coli*, *Pasteurella, Hemophilus spp.*) - False positives
- **Choice of cut-off (continuous tests)** – Sp increases with increase in cut-off (vice-versa)



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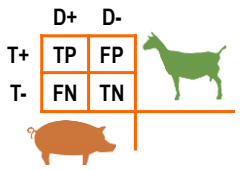
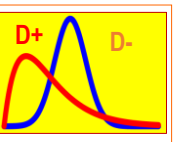


Diagnostic Tests:
(Sensitivity and Specificity)



Answers 4 questions for the clinician

Chance that a **diseased** individual will test positive?

Chance that a **diseased** individual will test negative?

Chance that a **non-diseased** individual will test positive?

Chance that a **non-diseased** individual will test negative?

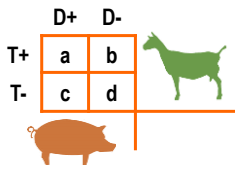
NOT HELPFUL!

Clinician asks:

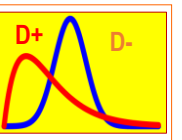
If an individual **tests positive,** chance that it is diseased (or non-diseased)?

If an individual **tests negative,** chance that it is non-diseased (or diseased)?

17



Diagnostic Tests
Characteristics

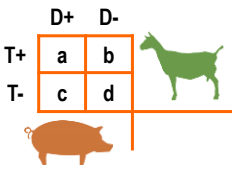


Positive Predictive Value (PPV):

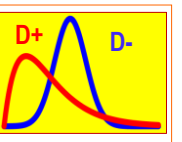
- Probability that an individual that tests positive is truly diseased = P(D+|T+)
- Proportion of T+ that are truly D+
- Range 0 - 1 (0 – 100%)
- Gold Standard: PPV = 1

$$PPV = \frac{\text{Number of T+ individuals that are D+}}{\text{Total number of D+ individuals}} = \frac{a}{a+b} = \frac{TP}{TP+FP}$$

18



Diagnostic Tests
(Characteristics)

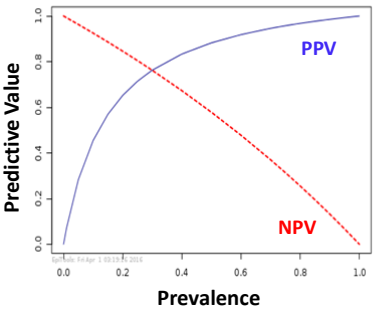


PPV: Dependent on Se, Sp and Prevalence (P).

$$PPV = \frac{P \times Se}{(P \times Se) + [(1 - P) \times (1 - Sp)]}$$

Disadvantage: For fixed Se, Sp very dependent on prior probability of outcome (i.e., prevalence)

Advantage: Preserves diagnostic logic order



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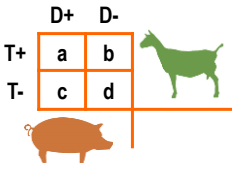
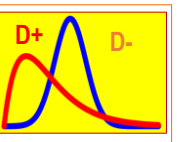


Diagnostic Tests
(Characteristics: Predictive Values)

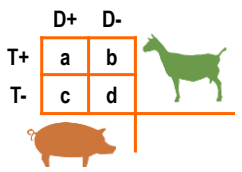


Negative Predictive Value (NPV):

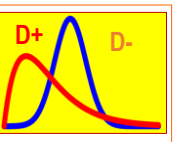
- Probability that an individual that tests negative is truly non-diseased = Prob (D-|T-)
- Proportion of T- that are truly D-
- Range 0 -1 (0 – 100%)
- Gold Standard: NPV = 1

$$NPV = \frac{\text{Number of T- individuals that are D-}}{\text{Total number of T- individuals}} = \frac{d}{c + d} = \frac{TN}{TN + FN}$$

20



Diagnostic Tests
(Characteristics: Predictive Values)

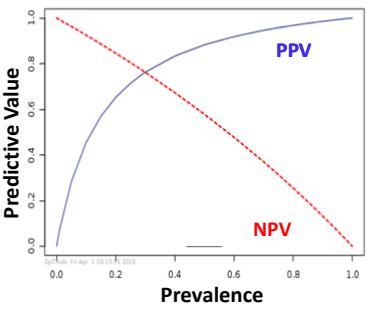


NPV: Dependent on Se, Sp and Prevalence (P)

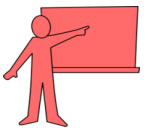
$$NPV = \frac{(1 - P) \times Sp}{[(1 - P) \times Sp] + [P \times (1 - Se)]}$$

Disadvantage: For fixed Se, Sp, very dependent on prior probability of outcome (i.e., prevalence)

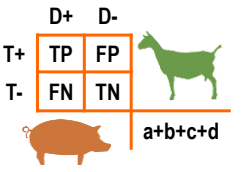
Advantage: Preserves diagnostic logic order



21



Diagnostic Tests:
(Likelihood Ratios)



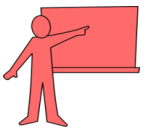
$$LR+ = \frac{Se}{1 - Sp}$$

- Chance of diseased animal tests positive divided by chance that a non-diseased animal tests positive
- How many **more times** will a diseased animal test positive than a non-diseased animal
- Range: 1 to ∞
- Unique for each test
- Association between D+ and T+ ↑ → LR+ ↑

$$LR- = \frac{1 - Se}{Sp}$$

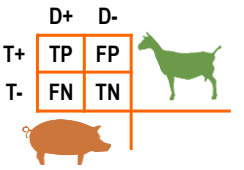
- Chance of diseased animal tests negative divided by chance that a non-diseased animal tests negative
- How many **more times** will a diseased animal test negative than a non-diseased animal
- Range: 0 to 1
- Unique for each test
- Association between D- and T- ↑ → LR+ ↓

22



Fagan's Nomogram:

Fagan (NEJM, 1975)



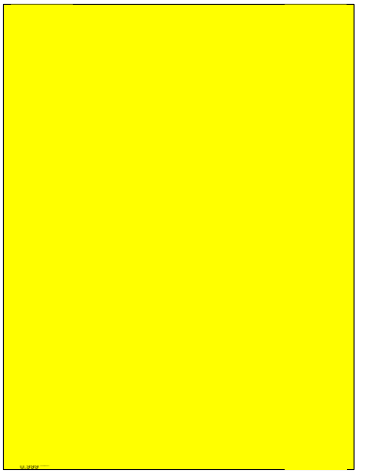
Fagan's Nomogram

- Two – dimensional, graphical analogue computation device
- **Three scales:**

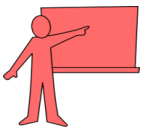
  i. **Pre-test probability** = Opinion before testing

  i. **Likelihood ratio** = How much more likely is a D+ to have a given test result than a D-

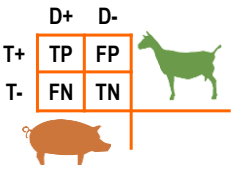
  iii. **Post-test probability** = Opinion after testing



23



Fagan's Nomogram:
(Evidence-Based Medicine)



Fagan's Nomogram:

Two important elements:

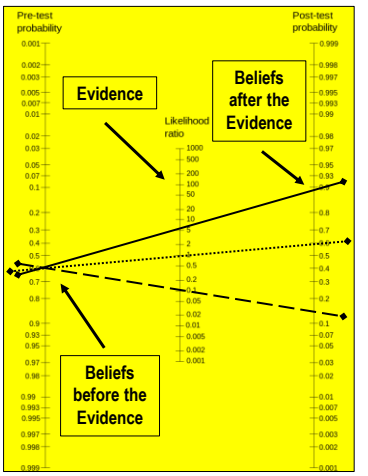
i. Clinical expertise – Prior beliefs, opinion

+

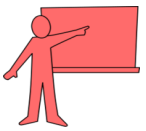
ii. External sources – Evidence: results of the diagnostic test

⬇

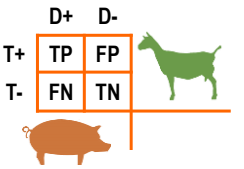
Diagnosis = Final beliefs, opinion



24



Fagan's Nomogram:
(Evidence-Based Medicine)

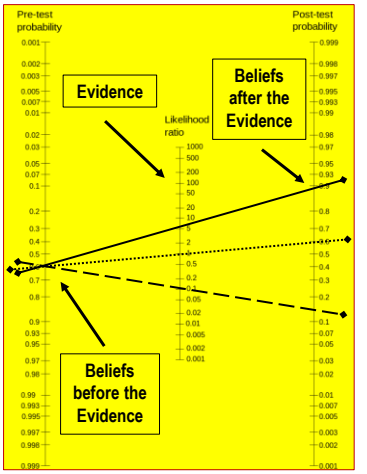


Fagan's Nomogram

- Links pre-test probabilities (prevalences) to post-test probabilities

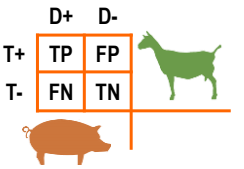
Pre-Test Odds × LR = Post-Test Odds

$$\frac{P_{Pre\text{-}Test}}{1 - P_{Pre\text{-}Test}} \times LR = \frac{P_{Post\text{-}Test}}{1 - P_{Post\text{-}Test}}$$



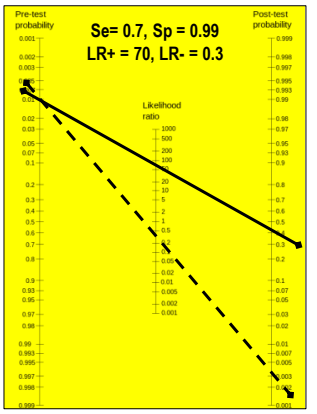
25

Covid -19 (Hypothetical Example)

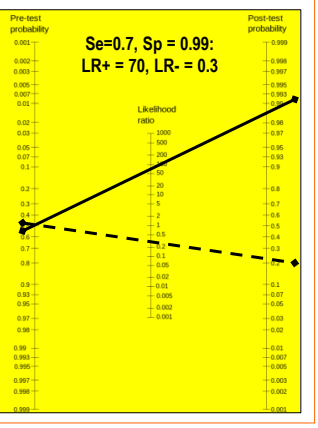


Interpretation depends on pre-test probability

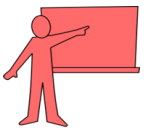
Low Exposure Risk



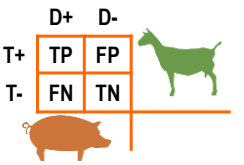
High Exposure Risk



26



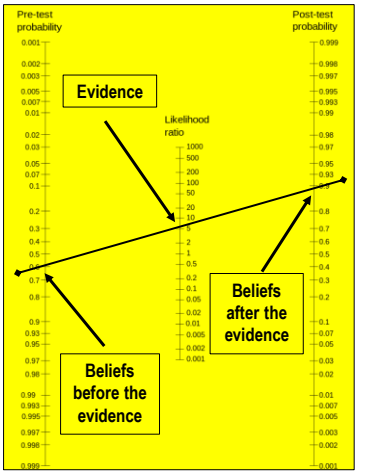
Diagnostic Tests
(Likelihood ratios, Nomogram)



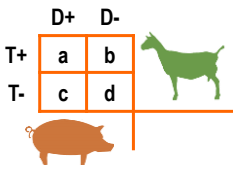
Experience, Skill
- Prior beliefs regarding disease

Diagnostic tests: Likelihood Ratios
- Weight of (external) evidence

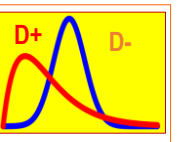
Clinical Nomogram
- **Initial Beliefs + Weight of Evidence = Final beliefs**
- Helps to concretize assumptions
- Formalizes cognitive processes
- Helps in the recognition of illogical thought processes
- Easy.
- No need for knowledge of math behind it (Bayes theorem)
- Easy communication with client



27



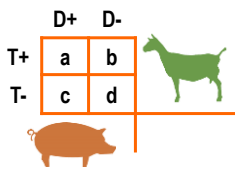
Diagnostic Test: Applications
(True and Apparent Prevalence)



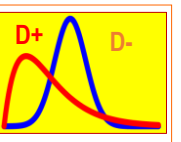
True and Apparent (or Test) Prevalence

- Test imperfect ⇒ Disease misclassification
- Some D+ classified as D- (FN)
- Some D- classified as D+ (FP)

28



Diagnostic Test Applications
(True and Apparent Prevalence)



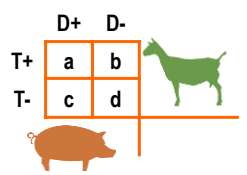
True and Apparent (or Test) Prevalence.

$$\text{Apparent Prevalence (AP)} = \frac{\text{Number T+ @ time "t"}}{\text{Total population @ risk @ time "t"}}$$

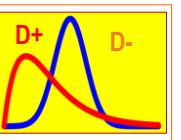
$$AP = \frac{\text{Number of T+ @ time "t"}}{\text{Total No. Tested @ time "t"}}$$

$$AP = \frac{a + b}{a + b + c + d}$$

29



Diagnostic Test Applications
(True and Apparent Prevalence)

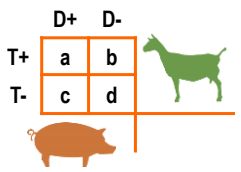


True Prevalence (TP):

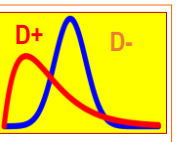
- Latent (Unobserved) Variable
- TP ≠ AP (except for Gold Standard)
- Can be > AP or < AP

$$TP = \frac{AP + Sp - 1}{Se + Sp - 1}$$

30



Diagnostic Test Applications
(True and Apparent Prevalence)



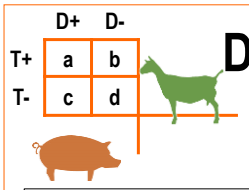
True and Apparent (or Test) Prevalence.

$$TP = \frac{\text{Number having outcome @ time "t"}}{\text{Total population @ risk @ time "t"}}$$

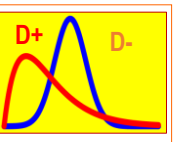
$$TP = \frac{\text{No. of D+ @ time "t"}}{\text{Total No. Tested @ time "t"}}$$

$$TP = \frac{a + c}{a + b + c + d}$$

31



Diagnostic Test Applications
(True and Apparent Prevalence)

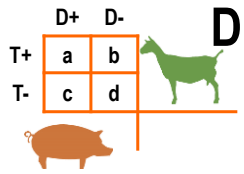


Estimates of true prevalence of F. hepatica infection corresponding to combinations of sensitivity (0.61-0.75), specificity (0.85-0.91) and AP values of 0.21 and 0.21

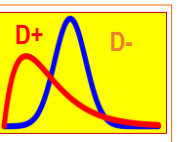
	Specificity									
	Apparent Prevalence = 0.21					Apparent Prevalence = 0.26				
Sensitivity	**0.85**	**0.87**	**0.88**	**0.89**	**0.91**	**0.85**	**0.87**	**0.88**	**0.89**	**0.91**
0.61	0.13	0.17	0.18	0.20	0.23	0.24	0.27	0.29	0.31	0.33
0.63	0.13	0.16	0.18	0.19	0.22	0.23	0.26	0.27	0.30	0.31
0.65	0.12	0.15	0.17	0.19	0.21	0.22	0.25	0.26	0.28	0.30
0.67	0.12	0.15	0.16	0.18	0.21	0.21	0.24	0.25	0.26	0.29
0.68	0.11	0.15	0.16	0.18	0.20	0.20	0.23	0.25	0.26	0.28
0.69	0.11	0.14	0.16	0.17	0.20	0.20	0.23	0.25	0.26	0.28

In shaded areas TP > AP (Carrol et. al (2017) PVM. 144: 57-65)

32



Diagnostic Test Applications
(Screening and Confirmatory Tests)

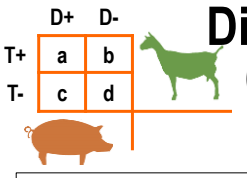


Screening Tests:

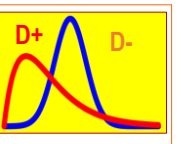
- Detect asymptomatic individuals
- High false negative cost: (Covid-19, bTB, Breast Cancer, HIV-Aids, Strangles, MAP)
- Se high (as possible)
- Rule out test negatives
- FN~0
- Cheaper (hopefully!)

	D+	D-
T+	TP	FP
T-	**FN~0**	FN

33



Diagnostic Test Applications
(Screening and Confirmatory Tests)



Diagnostic Tests:

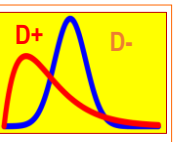
- Final diagnosis (previous T+'s)
- High FP cost: Avoid unnecessary culling, isolation, costly or (painful) treatment (Cancer, HIV-AIDs)
- Sp high (as possible)
- Rule in Test positives
- FP~0

	D+	D-
T+	TP	**FP~0**
T-	FN	TN

34

	D+	D-
T+	a	b
T-	c	d

Diagnostic Test Applications
(Screening and Confirmatory Tests)



Example:

200 Individuals, TP = 40/200 = 20%

- Test A: Se = 98%, Sp = 90%, €15
- Test B: Se = 85%, Sp = 99%, €40

Phase I (Screening)

- Only 55 test positive ⇒ Phase II

Phase II (Confirmation)

- 33/39 D+ test positive ⇒ isolated, treated, culled

- Assuming cure, TP ⇒ 7/200 = 3.5%
- Assuming culling, TP ⇒ 7/167 = 4.2%

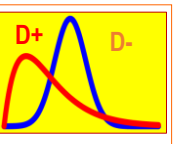
I	D+	D-	
T+	39	16	55
T-	1	144	145
	40	160	**200**

II	D+	D-	
T+	33	0	33
T-	6	16	22
	39	16	55

35

	D+	D-
T+	a	b
T-	c	d

Diagnostic Test Applications
(Series and Parallel)



Series

	Test I	Test II
Positive	+	+
Negative	+	-
	-	+
	-	-

Parallel

	Test I	Test II
Positive	+	+
	+	-
	-	+
Negative	-	-

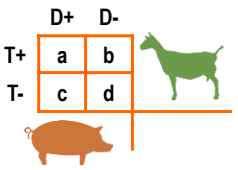
Series

- Joint Se lower
- Joint Sp higher
- Independence ↑ ⇒ Net difference ↑

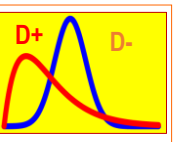
Parallel

- Joint Se higher
- Joint Sp lower
- Independence ↑ ⇒ Net difference ↑

36



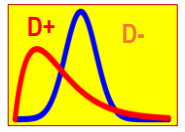
Diagnostic Tests
(Applications: Parallel Testing)



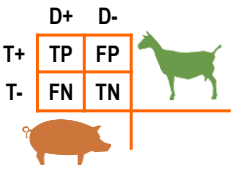
		Strangles Status S. equi+	S. equi-	
Antigen A	+	66	1	Se = 74.2%,
	-	23	138	Sp = 99.3%
	Total	89	139	
Antigen C	+	53	0	Se = 59.6%,
	-	36	139	Sp = 100.0%
Total		89	139	
Antigen A & C	+	83	1	Se = 93.3%,
	-	6	138	Sp = 99.3%
Total		89	139	

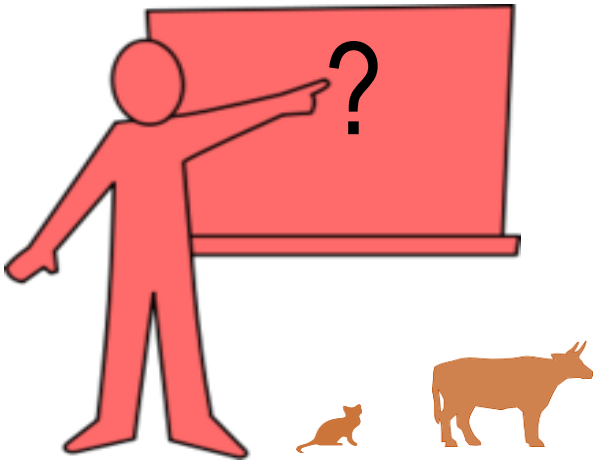
Taken from Robinson et. al (2013), TVJ 197:188-191

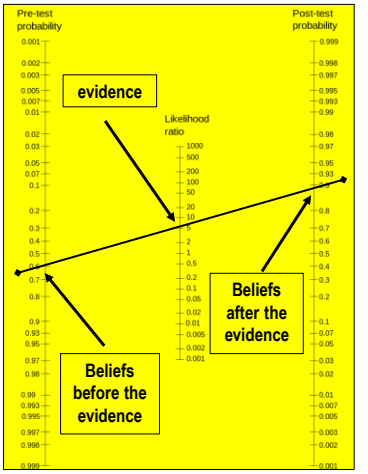
37



Diagnostic Tests







38