VALITEST webinar series and training activities

Using estimates gained during test performance studies

30th – 31st March 2020

Roy Macarthur

Fera

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 773139

TPS estimates and fitness for purpose

- We can use TPS results to predict how a method is likely to perform
- Combined with the cost of testing we can predict fitness for purpose
- This introduces the prediction of fitness for purpose for a number of types of scenario that should cover most cases

Valitest

Fitness for PURPOSE

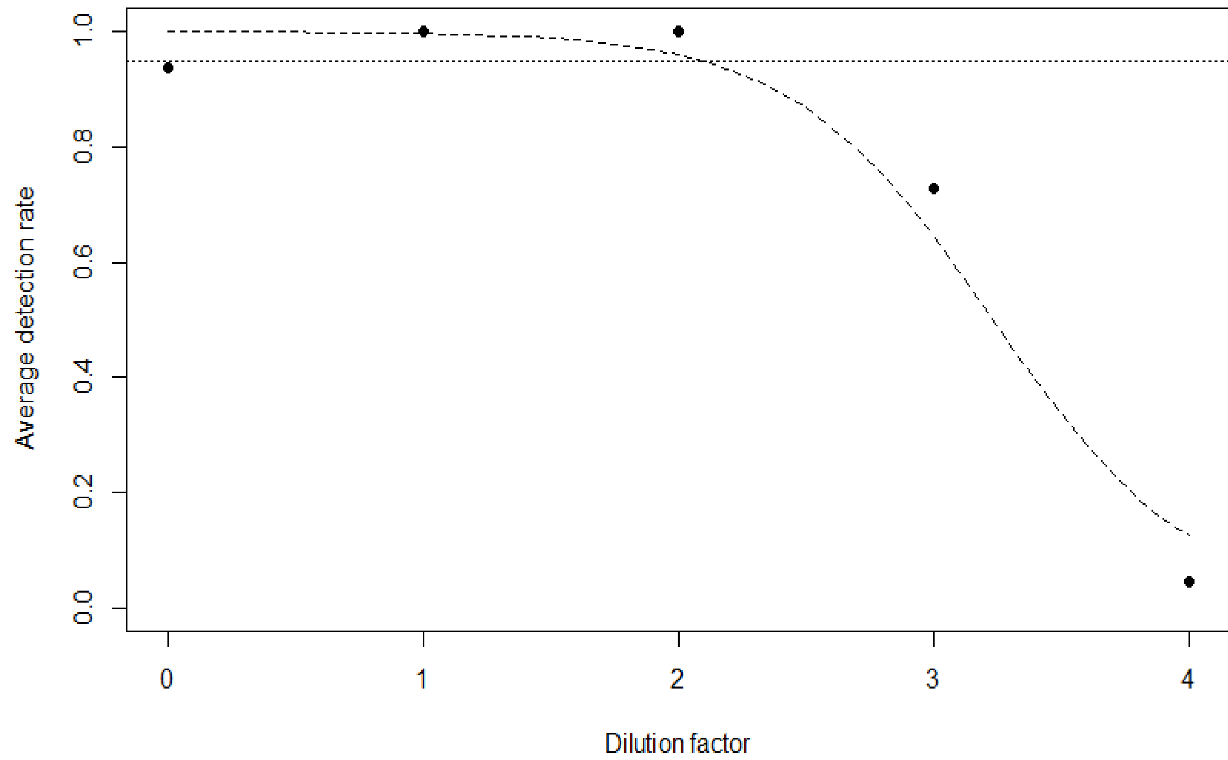
- Early detection: detection at lowest prevalence
- Delineation of outbreak: detection at lowest prevalence

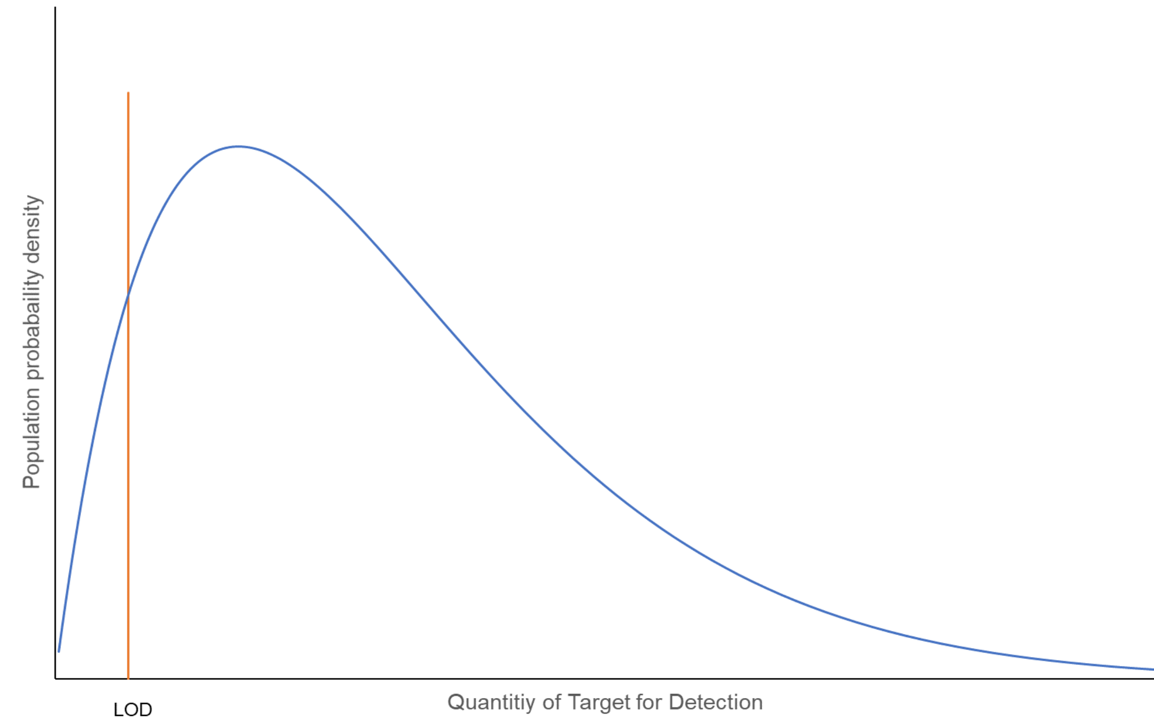
- “Eradication”: all negative results are correct

- Monitoring presence: most accurate estimate of prevalence

Valitest

Information from TPSs





Valitest

Information from TPSs

	Method 1	Method 2	Method 3
Transferable	✔	✔	✔
Robust	✔	✔	✔
Timely	✔	✔	✘
Diagnostic sensitivity	Se_1	Se_2	Se_3
Diagnostic Specificity	Sp_1	Sp_2	Sp_3
Cost per test	L_1	L_2	L_3

Valitest

Early detection

- A pathogen may be present.
- If it is present it is still at a low prevalence but growing exponentially with rate R per time
- We have a perfect test with 100% diagnostic specificity and 100% diagnostic sensitivity; we have a test budget of B per time
- What might the highest prevalence (with 95% confidence) be when we first detect the pathogen using a test with cost L

$$N = \frac{B}{L} \qquad prev_{95} = \frac{3.R}{N}$$

Valitest

Early detection

- A pathogen may be present.
- If it is present it is still at a low prevalence but growing exponentially with rate R per time
- We have a ~~perfect~~ test with 100% diagnostic specificity and a diagnostic sensitivity of Se; we have a test budget of B per time
- What might the highest prevalence (with 95% confidence) be when we first detect the pathogen using a test with cost L

$$N = \frac{B}{L} \qquad prev_{95} = \frac{3.R}{N.Se}$$

Valitest

Early detection

- A pathogen may be present.
- If it is present it is still at a low prevalence but growing exponentially with rate R per time
- We have a test with a diagnostic specificity Sp and a diagnostic sensitivity of Se; we have a test budget of B per time. If we get a false positive there is a cost F to resolve it
- What might the highest prevalence (with 95% confidence) be when we first detect the pathogen using a test with cost L

$$N = \frac{B}{L + F.(1 - Sp)} \qquad prev_{95} = \frac{3.R}{N.Se}$$

Valitest

Early detection

- A pathogen may be present.
- If it is present it is still at a low prevalence but growing exponentially with rate R per time
- We have a test with a diagnostic specificity Sp and a diagnostic sensitivity of Se; we have a test budget of B per time. If we get a false positive there is a cost F to resolve it
- What might the highest prevalence (with 95% confidence) be when we first detect the pathogen using a test with cost L

$$N = \frac{B}{L + F.(1 - Sp)} \qquad prev_{95} = \frac{3.R}{N.Se} \qquad N_{eff} = \frac{B.Se}{L + F.(1 - Sp)}$$

Valitest

Delineation of an outbreak

- A pathogen may be present in an area.
- If it is present it is ~~still~~ at a low prevalence ~~but growing exponentially with rate R per time~~
- We have a test with a diagnostic specificity Sp and a diagnostic sensitivity of Se; we have a test budget of B per area. If we get a false positive there is a cost F to resolve it
- What might the highest prevalence (with 95% confidence) be in an area in which we don't detect the pathogen using a test with cost L

$$N = \frac{B}{L + F.(1 - Sp)} \qquad prev_{95} = \frac{3}{N.Se} \qquad N_{eff} = \frac{B.Se}{L + F.(1 - Sp)}$$

Valitest

Delineation of an outbreak

- A pathogen may be present in an area.
- If it is present it is at a low prevalence.
- We have a test with a diagnostic specificity Sp and a diagnostic sensitivity of Se; we have a test budget of B per area. If we get a false positive there is a cost F to resolve it
- What might the highest prevalence (with 95% confidence) be in an area in which we don't detect the pathogen using a test with cost L

$$N = \frac{B}{L+F.(1-Sp)} \qquad prev_{95} = \frac{3}{N.Se} \qquad N_{eff} = \frac{B.Se}{L+F.(1-Sp)}$$

Valitest

Eradication

- Applicable where there a small number of valuable plants at risk.
- We need to remove every infected individual
- It is nice if we can also save some uninfected individuals
- Untested plants are assumed infected
- We need high confidence about each negative test result; a sufficiently high negative predicative value

$$NPV = \frac{expected\ number\ true\ negative}{expected\ number\ true\ negative + expected\ number\ false\ negative}$$

$$\frac{expected\ number\ true\ negative}{expected\ number\ false\ negative} = \frac{1 - prev}{prev} \times \frac{Sp}{1 - Se}$$

Valitest

Eradication

- Applicable where there a small number of valuable plants at risk.
- We need to remove every infected individual
- It is nice if we can also save some uninfected individuals
- Untested plants are assumed infected
- We need high confidence about each negative test result; a sufficiently high negative predicative value

$$NPV = \frac{expected\ number\ true\ negative}{expected\ number\ true\ negative + expected\ number\ false\ negative}$$

$$\frac{expected\ number\ true\ negative}{expected\ number\ false\ negative} = \frac{1 - prev}{prev} \times \frac{Sp}{1 - Se}$$

Valitest

Eradication II

- Applicable where there a small number of valuable plants at risk.
- We need to remove every infected individual
- It is nice if we can also save some uninfected individuals
- Untested plants are assumed infected
- We need high confidence about ALL negative test results; a sufficiently high negative predicative value for zero infected among all negative test results

$$NPV_{ALL} = \left(\frac{number\ true\ neg.}{number\ true\ neg. + number\ false\ neg}\right)^{N\ neg.results}$$

Valitest

Probability of NO false negatives where all results are negative

- Upper limit (95% confidence) for prevalence = 3/N.Se

- HENCE!

- $NPV_{ALL} > e^{(3-3/Se)}$ for N>30

- Approximation: maximum (95% confidence) probability of there being ANY false positives among all of the tested plants giving a negative result is 3 x the false positive rate of the test: $NPV_{ALL} > 1 - 3.(1 - Se)$ for N>30 and Se>0.85 IF ALL TESTS ARE NEGATIVE

Valitest

Monitoring prevalence

- We want to estimate the prevalence in a population
- Assume we can sample at random!
- We use a perfect method to detect a pathogen in each plant: 100% diagnostic specificity, 100% diagnostic sensitivity
- We detect x positive plants out of n tested

Valitest

x positive out of n tested: perfect method

Result	Estimate	Lower 95% confidence	Upper 95% confidence
0<x<n	x/n	((x+1.64)/(n+2.71))-1.64*sqrt(((x+1.64)/(n+2.71)) *(1-((x+1.64)/(n+2.71)))/(n+2.71))	((x+1.64)/(n+2.71))+1.64*sqrt(((x+1.64)/(n+2.71)) *(1-((x+1.64)/(n+2.71)))/(n+2.71))

Agresti-Coull method (for n>30)

Brown LD, Cai TT, DasGupta A (2001) Interval Estimation for a Binomial Proportion, *Statistical Science*, **16 (2)** 101 - 133

Valitest

x positive out of n tested: perfect method

Result	Estimate	Lower 95% confidence	Upper 95% confidence
x=0	x/n	0	1-0.05^(1/n)
0<x<n	x/n	BETAINV(0.05,x+0.5,n-x+0.5)	BETAINV(0.95,x+0.5,n-x+0.5)
x=n	x/n	0.05^(1/n)	1

Modified Jeffreys method (for any n)

Brown LD, Cai TT, DasGupta A (2001) Interval Estimation for a Binomial Proportion, *Statistical Science*, **16 (2)** 101 - 133

x positive out of n tested: perfect method

Outcome	Estimate	95% Confidence interval Lower	Upper
x=0	x/n	0	1-0.05^(1/n)
0<x<n	x/n	BETAINV(0.025,x+0.5,n-x+0.5)	BETAINV(0.975,x+0.5,n-x+0.5)
x=n	x/n	0.05^(1/n)	1

Upper limit for prevalence (95% confidence) if we don't find any positives

$$1-0.05^{\frac{1}{n}} \approx \frac{3}{n} \quad for\ n\ more\ than\ 30$$

Valitest

x positive out of n tested: sensitivity =Se, specificity=Sp

Model:

- x is a random observation from a binomial distribution with size n and probability p
- $p = prev \, . Se \; + \; (1 - prev).(1 - Sp)$
- prev is described by a beta distribution, initially a flat uniform distribution (with shape parameters (1,1))

- Prevalence =…the prevalence package in R can do all of the hard work
- Speybroeck N, Devleesschauwer B, Joseph L, Berkvens D (2013) Misclassification errors in prevalence estimation: Bayesian handling with care. Int J Public Health 58:791-795

Valitest

Examples: early detection; delineation; eradication; monitoring prevalence

- Three validated methods

Test	Cost	Performance	
		Sensitivity	Specificity
LFD	10	50%	99.5%
ELISA	30	95%	99.7%
DNA	100	99%	100%

- Cost associated with resolving a false positive in early detection and delineation scenarios equivalent to five DNA tests.

Valitest

Early detection

- Budget (B) = 10 000
- Growth rate (R) = 0.693 doubling every budget period

Test	Cost (L)	Performance Sensitivity (Se)	 Specificity (Sp)	N	N_{eff}	P_{rev95}
LFD	10	50%	99.5%	800.0	400.0	0.52%
ELISA	30	90%	99.7%	317.5	285.7	0.73%
DNA	100	99%	100%	100.0	99.0	2.10%

$$N = \frac{B}{L+F.(1-Sp)} \qquad prev_{95} = \frac{3.R}{N.Se} \qquad N_{eff} = \frac{B.Se}{L+F.(1-Sp)}$$

Valitest

Outbreak delineation

- Budget (B) = 1000 per area

Test	Cost (L)	Performance Sensitivity (Se)	 Specificity (Sp)	N	N_{eff}	P_{rev95}
LFD	10	50%	99.5%	80.0	40.0	7.5%
ELISA	30	90%	99.7%	31.7	28.6	10.3%
DNA	100	99%	100%	10.0	9.9	30.3%

$$N = \frac{B}{L+F.(1-Sp)} \qquad prev_{95} = \frac{3}{N.Se} \qquad N_{eff} = \frac{B.Se}{L+F.(1-Sp)}$$

Valitest

Eradication

- Test budget (B) = 10 000
- + new options: a) just do nothing; b) burn everything

Test	Cost (L)	Performance	
		Sensitivity (Se)	Specificity (Sp)
NOTHING	0	0%	100%
LFD	10	50%	99.5%
ELISA	30	90%	99.7%
DNA	100	99%	100%
BURN	0	100%	0%

Valitest

Eradication

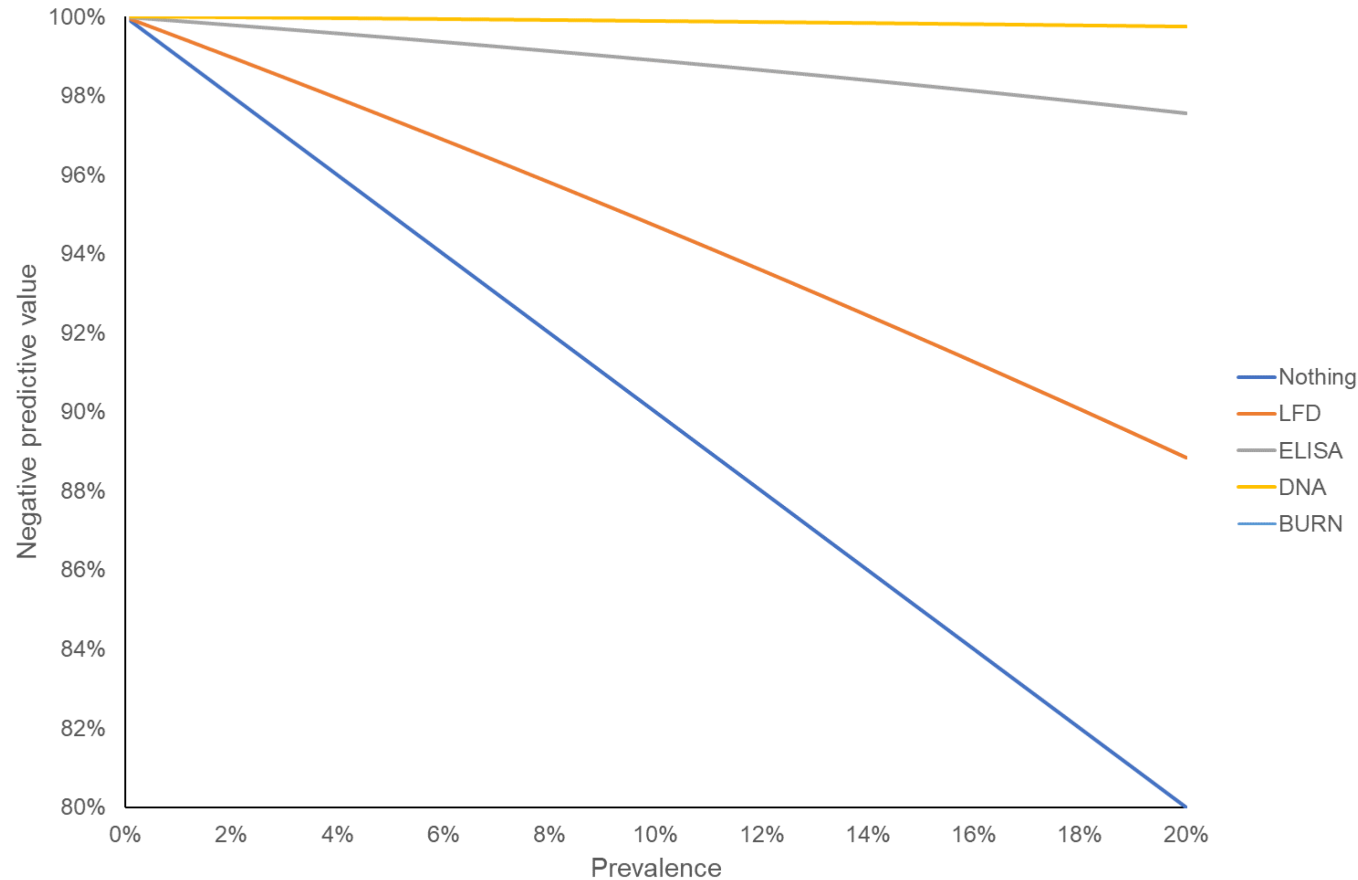
- Test budget (B) = 10 000
- + new options: a) just do nothing; b) burn everything

Test	Cost (L)	Performance Sensitivity (Se)	 Specificity (Sp)	Number	NP ratio
NOTHING	0	0%	100%	∞	1
LFD	10	50%	99.5%	800.0	1.99
ELISA	30	90%	99.7%	317.5	9.97
DNA	100	99%	100%	100.0	100
BURN	0	100%	0%	∞	NA

$$N = \frac{B}{L + F.(1 - Sp)} \qquad NPR = \frac{Sp}{1 - Se}$$

Valitest

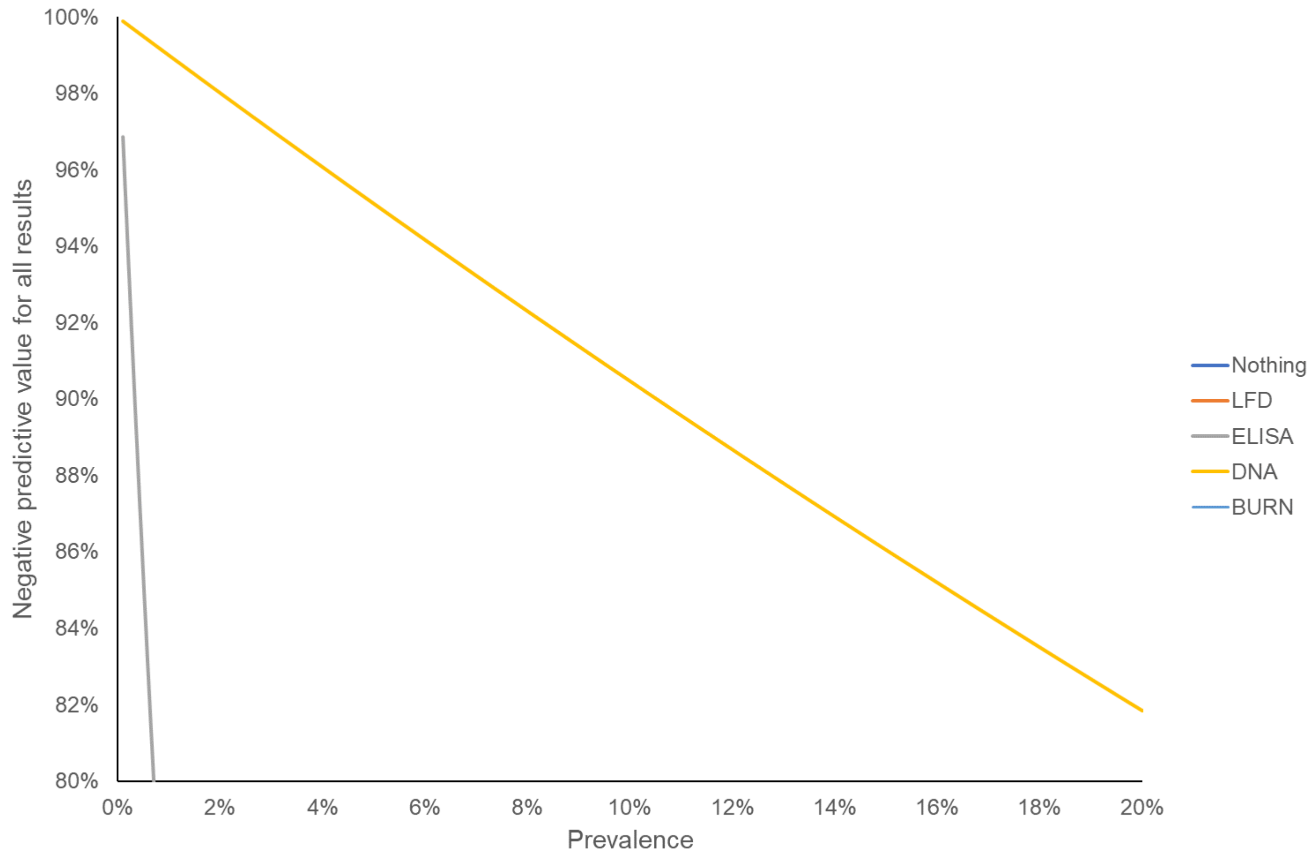
Eradication



$$N = \frac{B}{L + F.(1 - Sp)} \quad NPV = \frac{(1 - prev).Sp}{(1 - prev).Sp + prev.(1 - Se)}$$

Valitest

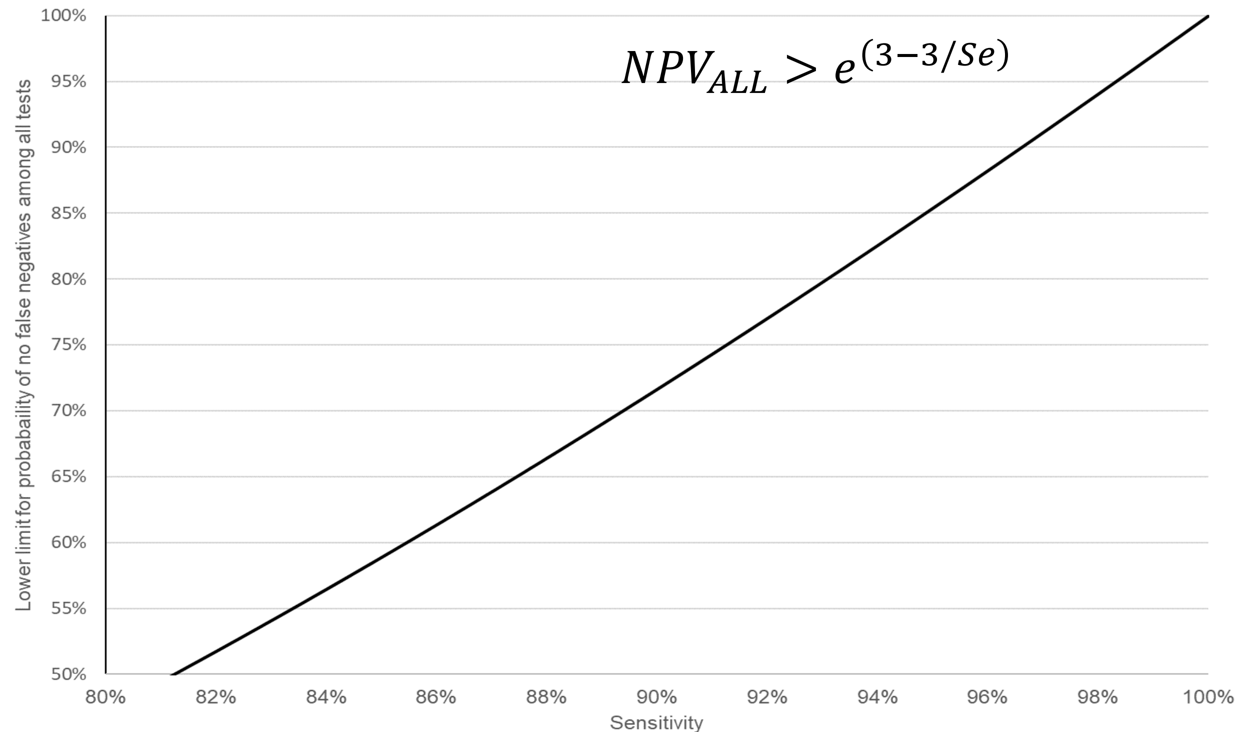
Eradication II



$$N = \frac{B}{L + F.(1 - Sp)} \quad NPV_{All} = \left(\frac{(1 - prev).Sp}{(1 - prev).Sp + prev.(1 - Se)} \right)^{number\ neg}$$

Valitest

Lower limit for probability of no false negatives where all tests are negative



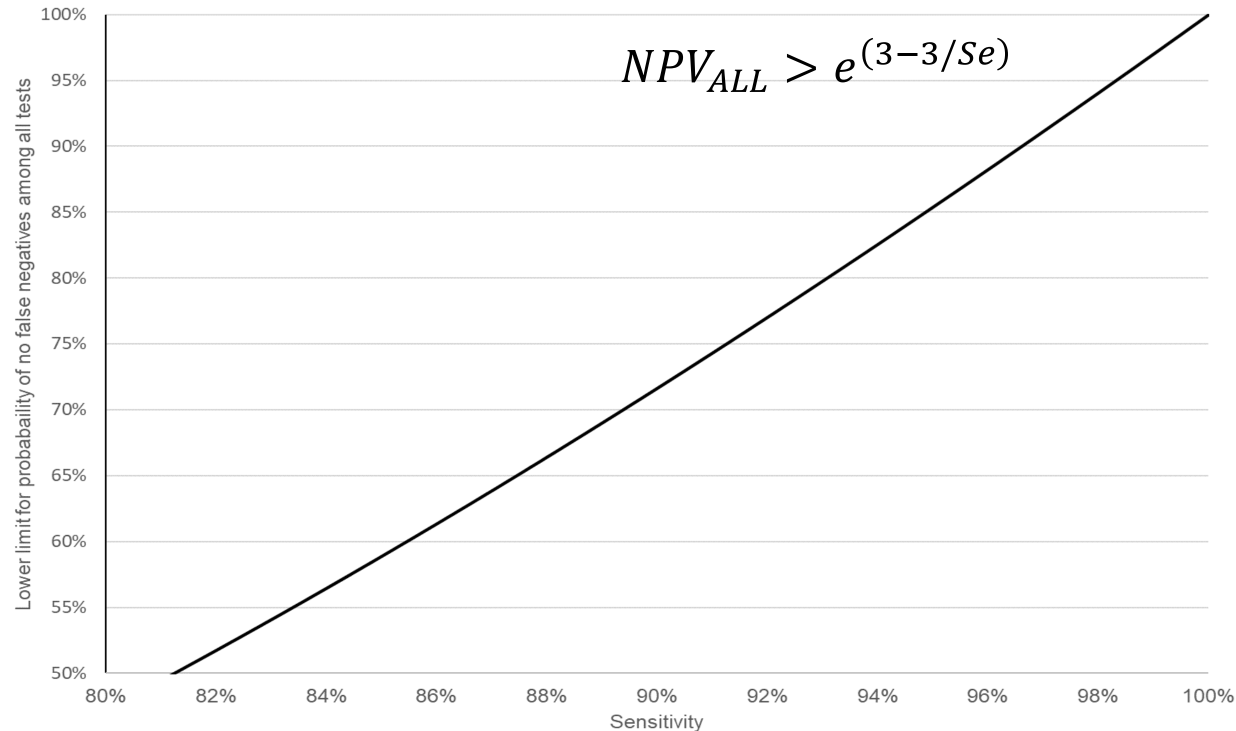
Approximately: $NPV_{ALL} > 1 - 3.(1 - \mathrm{Se})$

Where Se>0.85

Valitest

Lower limit for probability of no false negatives where all tests are negative

$NPV_{ALL} > 95\%$ where Se $> 98.4\%$

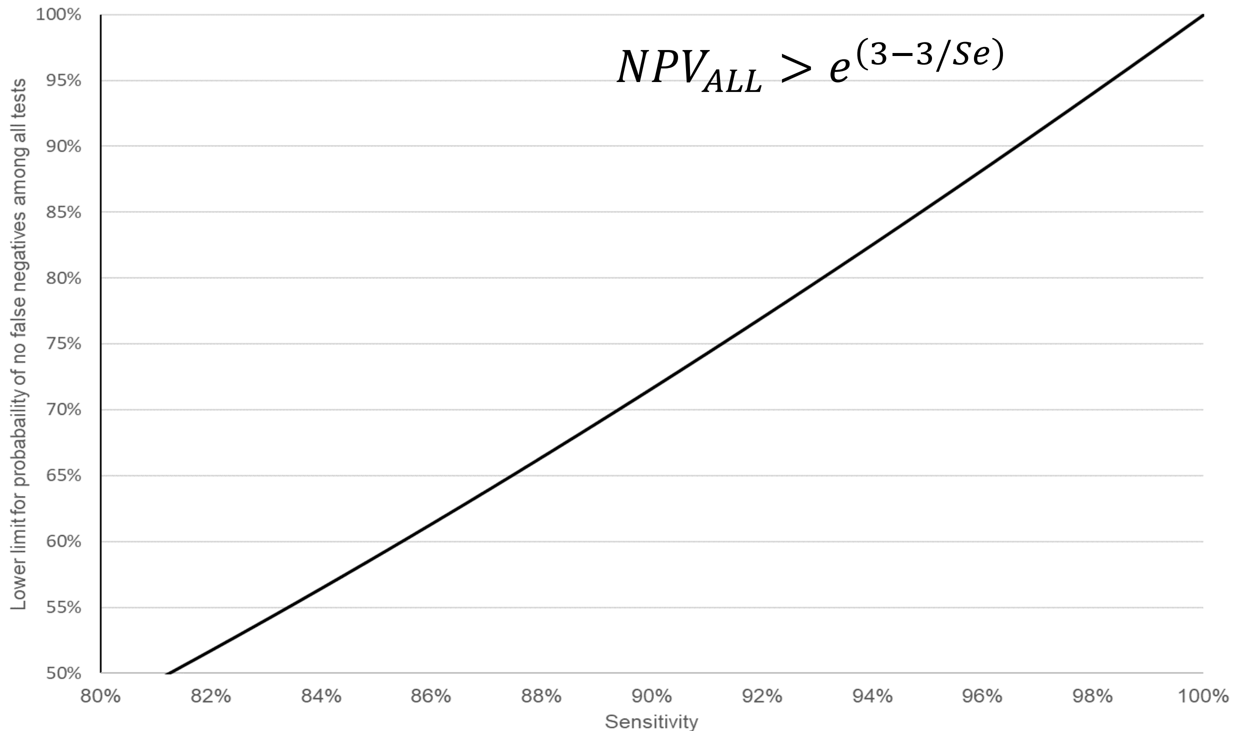


Approximately: $NPV_{ALL} > 1 - 3.(1 - \text{Se})$

Where Se>0.85

Valitest

Lower limit for probability of no false negatives where all tests are negative



Approximately: $NPV_{ALL} > 1 - 3.(1 - \mathrm{Se})$

Where Se>0.85

$NPV_{ALL} > 95\%$ where $\mathrm{Se} > 98.4\%$

A method showing no false negatives in 188 representative tests has sensitivity > 98.4%

IF you want to use a test to give high assurance about ALL tested samples Se>98.4% is a reasonable requirement

If you start seeing positives then you can't use testing alone to COMPLETELY separate all infected individuals from uninfected individuals in that population with high confidence

Valitest

Monitoring prevalence

- Several potential measures of measurement performance: e.g. standard error of estimates at a prevalence; width of confidence interval associated with estimates; power to detect difference between two different prevalences.
- Here we will use the prevalence package in R to estimate the width of a 95% confidence interval where the central estimate of prevalence is 1% and 5%

Valitest

Monitoring prevalence

- Testing budget £10 000; no retesting of positive results

Test	Cost (L)	Performance		N
		Sensitivity (Se)	Specificity (Sp)	
LFD	10	50%	99.5%	1000
ELISA	30	90%	99.7%	333
DNA	100	99%	100%	100.

Valitest

Monitoring prevalence

- Testing budget £10 000; no retesting of positive results

Test	Cost (L)	Performance Sensitivity (Se)	Specificity (Sp)	N	Central estimate 1% Pos.	Est	95% C.I.	
LFD	10	50%	99.5%	1000	9	0.9%	0.1%	2.5%
ELISA	30	90%	99.7%	333	4	1.0%	0.2%	3.0%
DNA	100	99%	100%	100	1	1.1%	0.2%	5.5%

```
>truePrev(x=9,n=1000,SE=0.5,SP=0.995)
    mean median  mode    sd  2.5% 97.5%
TP 0.010  0.010 0.009 0.006 0.001 0.025
```

Valitest

Monitoring prevalence

- Testing budget £10 000; no retesting of positive results

Test	Cost (L)	Performance Sensitivity (Se)	Specificity (Sp)	N	Central estimate 5% Pos.	Est	95% C.I.	
LFD	10	50%	99.5%	1000	30	5.0%	3.2%	7.6%
ELISA	30	90%	99.7%	333	16	5.0%	3.0%	8.2%
DNA	100	99%	100%	100	5	5.1%	2.2%	11.1%

Valitest

Monitoring prevalence

- Fixed number of tests: effect of test performance only

Test	Cost (L)	Performance Sensitivity (Se)	Specificity (Sp)	N	Pos.	Central estimate 1% Est	95% C.I.	
LFD	10	50%	99.5%	1000	9	0.9%	0.1%	2.5%
ELISA	30	90%	99.7%	1000	11	0.9%	0.4%	1.8%
DNA	100	99%	100%	1000	10	1.1%	0.6%	1.8%

Test	Cost (L)	Performance Sensitivity (Se)	Specificity (Sp)	N	Pos.	Central estimate 5% Est	95% C.I.	
LFD	10	50%	99.5%	1000	30	5.0%	3.2%	7.6%
ELISA	30	90%	99.7%	1000	48	5.0%	3.7%	6.7%
DNA	100	99%	100%	1000	50	5.0%	3.9%	6.6%

Valitest

Using TPS results to assess fitness for purpose

- Simple approximate formulas can be used to estimate cost-performance for early detection, delineation and tasks requiring confidence about individual results such as eradication

- Assessing cost performance of tests with imperfect sensitivity and specificity for estimating prevalence needs more advanced methods BUT! there are easy-to-use tools available

Valitest

Observations on test performance and fitness for purpose

- Early detection and delineation can be achieved most quickly with low sensitivity methods if they are cheap enough
- Where we require high confidence about each individual result this can occasionally be achieved with high sensitivity methods
- High confidence about ALL negative test results can only be achieved with high sensitivity methods AND where all results are negative
- With the right statistical tools methods with low sensitivity and imperfect specificity can provide accurate estimates of prevalence