

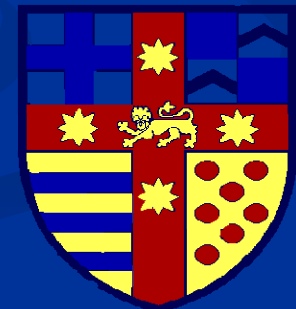
Statistics for Serology Kit Evaluations

David Dickeson

Centre for Infectious Diseases &
Microbiology Laboratory Services



Institute of Clinical Pathology
and Medical Research



“There are three kinds of lies:

Lies, damned lies and statistics.”

Benjamin Disraeli

as quoted by Mark Twain

Statistics

- Definitions
- Imperfect standards
- Prevalence
- Delta values
- Sample size
- Kit analysis: Ideal, Practical & Reality

Statistics

Disease Status

	Disease +	No Disease -
New +	TP	FP
Test -	FN	TN
Total	TP+FN	FP+TN

Definitions

- $\text{Sensitivity} = 100 \times \text{TP} / (\text{TP} + \text{FN})$
- $\text{Specificity} = 100 \times \text{TN} / (\text{FP} + \text{TN})$
- $\text{Positive predictive value} = 100 \times \text{TP} / (\text{TP} + \text{FP})$
- $\text{Likelihood ratio of pos.} = (1 - \text{sensitivity}) / \text{specificity}$
- $\text{Negative predictive value} = 100 \times \text{TN} / (\text{FN} + \text{TN})$
- $\text{Likelihood ratio of neg.} = \text{sensitivity} / (1 - \text{specificity})$
- $\text{Efficiency} = 100 \times (\text{TP} + \text{TN}) / (\text{TP} + \text{FP} + \text{TN} + \text{FN})$

1a. Effect of an Imperfect Standard

	Disease Status		Imperfect Standard	
	Disease	No Disease	+	-
New +	98	18	94	22
Test -	2	882	46	838
Total	100	900	140	860

True value of new kit

Sensitivity = $98/100 = 98\%$

Specificity = $882/900 = 98\%$

PPV = $98/116 = 84.5\%$

NPV = $882/884 = 99.8\%$

Perceived value

$94/140 = 67.1\%$

$838/860 = 97.4\%$

$94/116 = 81\%$

$838/884 = 94.8\%$

1b. Effect of an Imperfect Standard

	Reference Standard		Non-Reference Standard (Imperfect Standard)	
	Disease +	No Disease -	+	-
New +	44	1	40	5
Test -	7	168	4	171
Total	51	169	44	176

True value of new kit

Sens. = $44/51 = 86.3\%$

Spec. = $168/169 = 99.4\%$

Efficiency = $212/220 = 96.4\%$

Perceived value

Pos. agree = $40/44 = 90.9\%$

Neg. agree = $171/176 = 97.2\%$

Total = $211/220 = 95.9\%$

2. Test & Standard Flawed

	Disease Status		Imperfect Standard	
	Disease	No Disease	+	-
New +	85	135	175	45
Test -	15	765	5	775
Total	100	900	180	820

True value of new kit

$$\text{Sensitivity} = 85/100 = 85\%$$

$$\text{Specificity} = 765/900 = 85\%$$

$$\text{PPV} = 85/220 = 38.6\%$$

$$\text{NPV} = 765/780 = 98.1\%$$

Perceived value

$$175/180 = 97.2\%$$

$$775/820 = 94.5\%$$

$$175/220 = 79.5\%$$

$$775/780 = 99.4\%$$

3. Effect of Prevalence

	Disease Status (10%)		Disease Status (1%)	
	+	-	+	-
New +	9,500	4,500	950	4,950
Test -	500	85,500	50	94,050
Total	10,000	90,000	1,000	99,000

Sensitivity = $9500/10000 = 95\%$

$950/1000 = 95\%$

Specificity = $85500/90000 = 95\%$

$94050/99000 = 95\%$

PPV = $9500/14000 = 67.9\%$

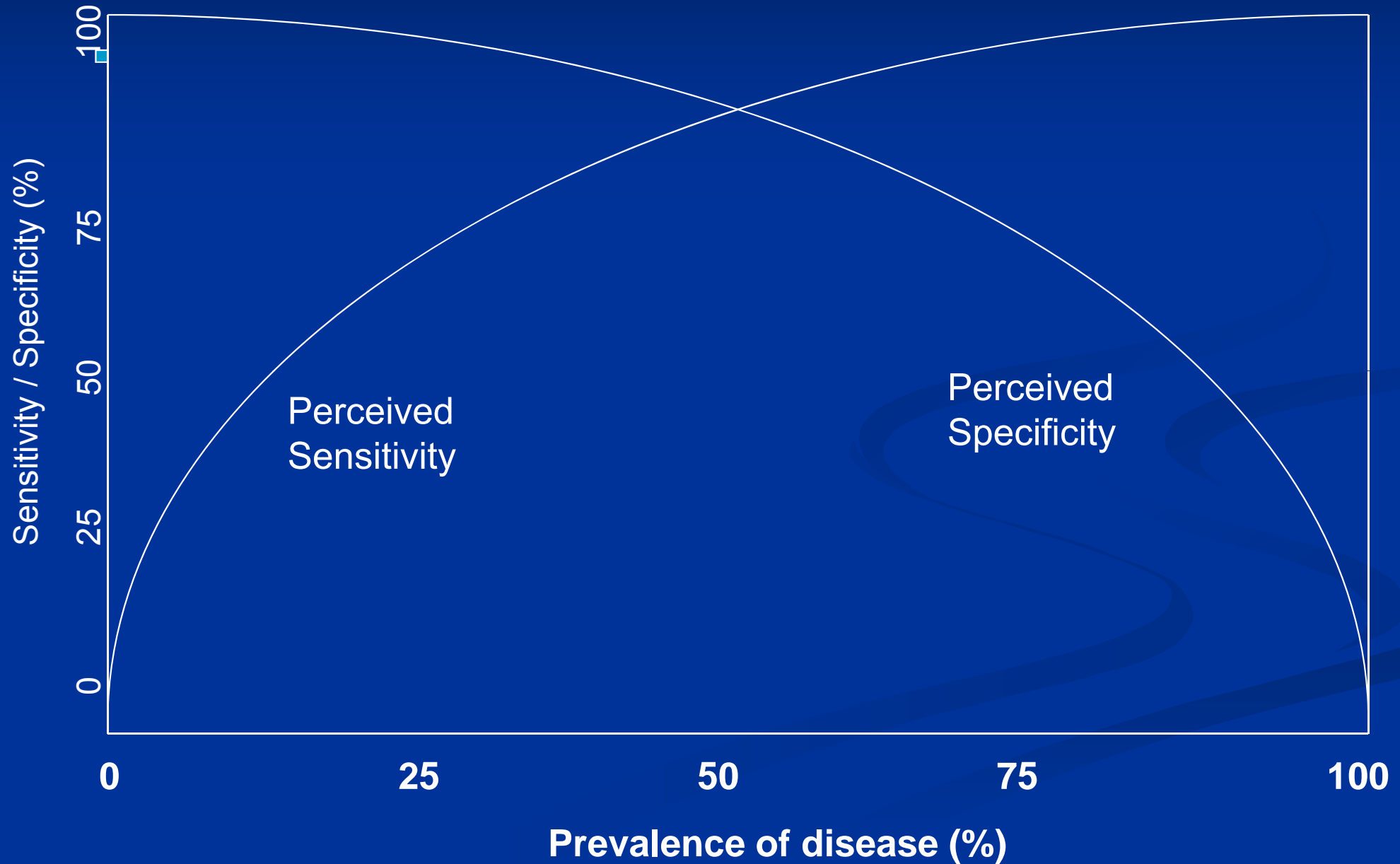
$950/5900 = 16.1\%$

NPV = $85500/86000 = 99.4\%$

$94050/94100 = 99.9\%$

Figure 1. Effect of Prevalence

Valentein, Am J Clin
Pathol 1990;93:252-8.

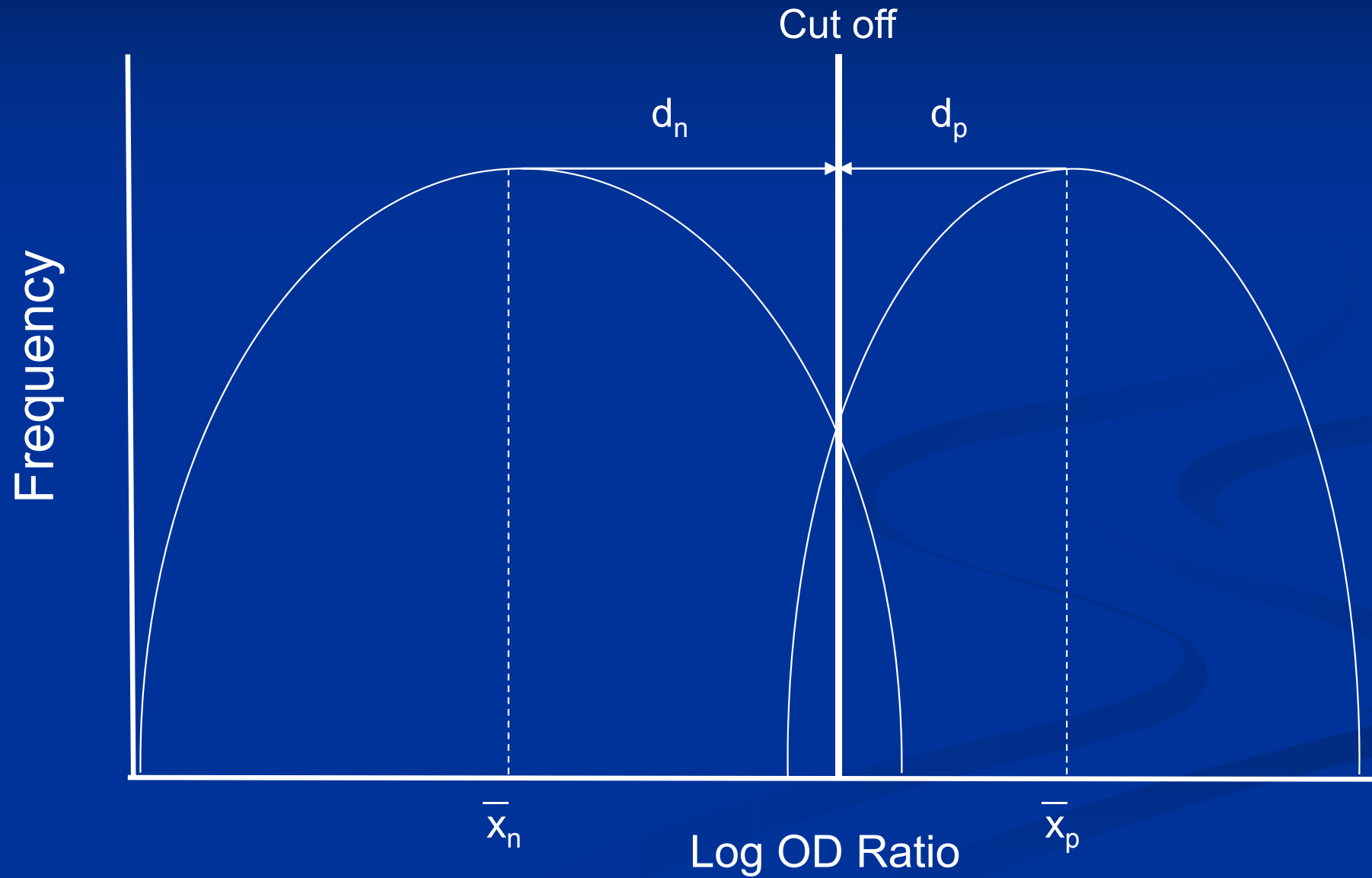


Delta values

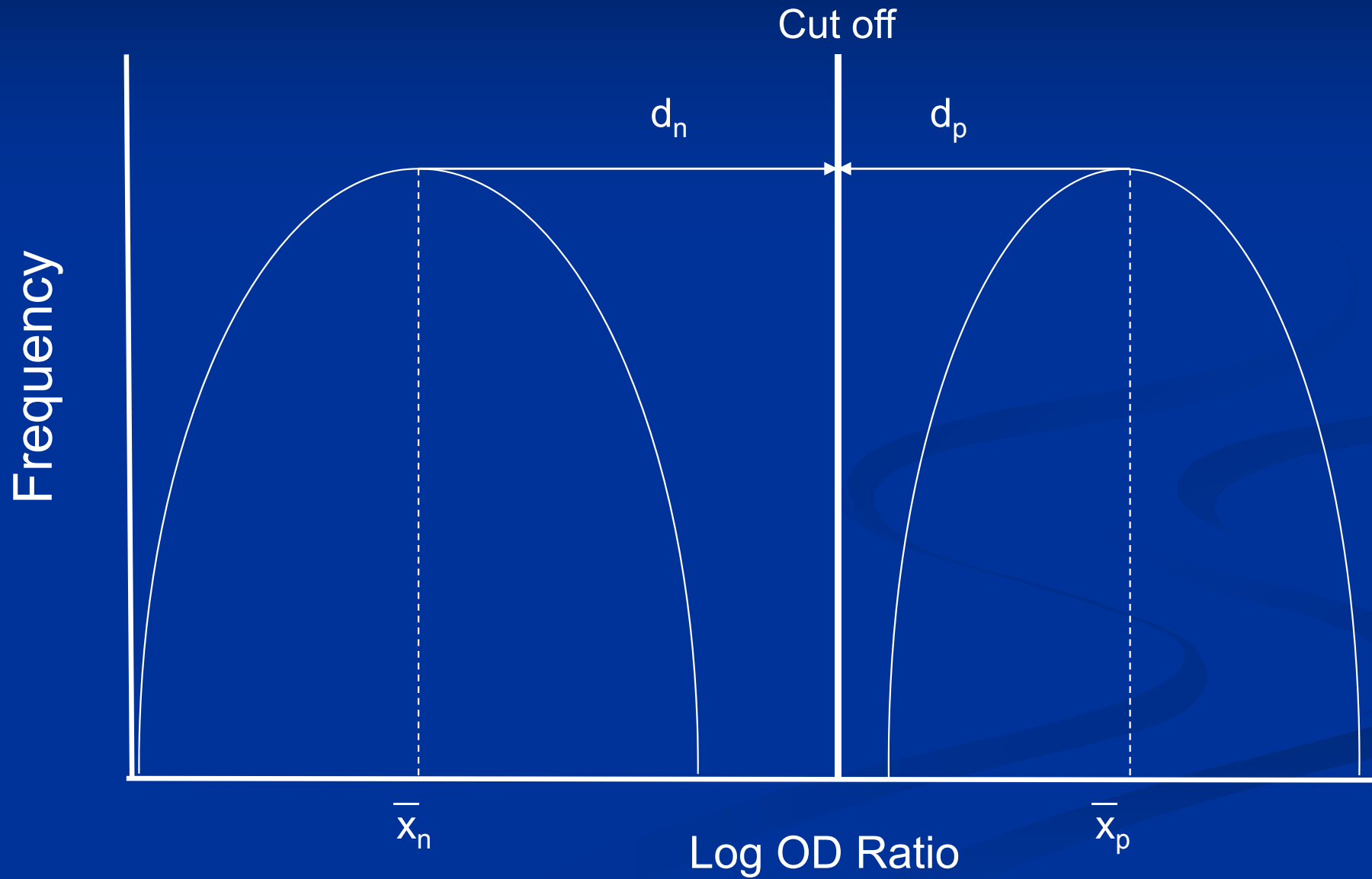
Separation of positive & negative populations using mean (\bar{x}) and standard deviation (sd).

- Distance (d) = mean OD ratio (\bar{x}) – Cut Off
- Delta (δ) = d / sd

Delta values: small



Delta values: large



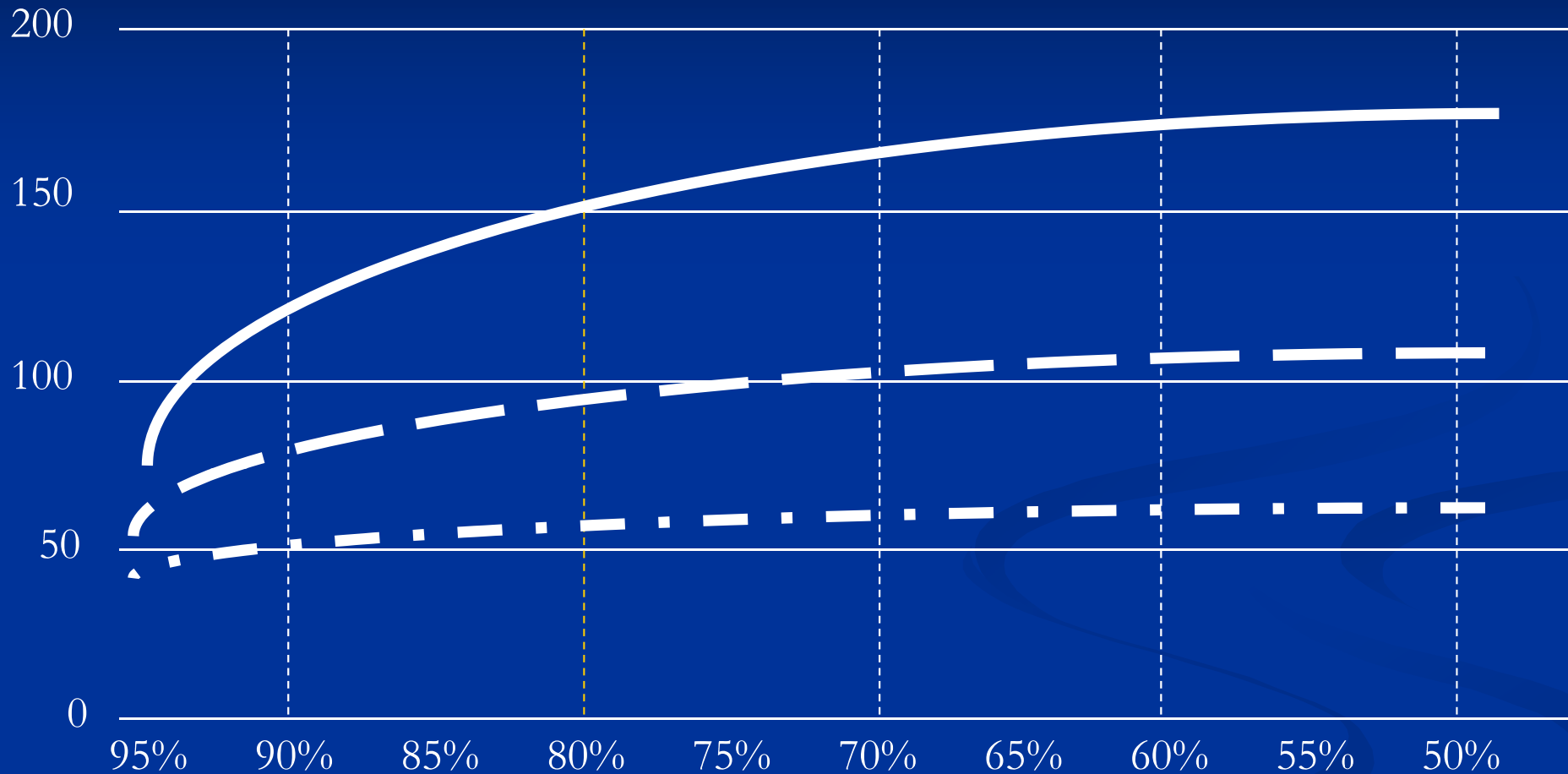
Sample size for two proportions

$d = p_1 - p_2$ at 80% power

p2	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
0.05	474	160	88	58	43	33	27	22	18	16
0.1	725	219	113	71	50	38	30	24	20	17
0.15	945	270	134	82	57	42	32	26	21	18
0.2	1134	313	151	91	62	45	34	27	22	18
0.25	1291	348	165	98	65	47	36	28	22	18
0.3	1416	376	175	103	68	48	36	28	22	18
0.35	1511	395	182	106	69	49	36	28	22	18
0.4	1573	407	186	107	69	48	36	27	21	17
0.45	1605	411	186	106	68	47	34	26	20	16
0.5	1605	407	182	103	65	45	32	24	18	-

Adapted from Fleiss 1981

Sample size for two proportions



Kit with greater Sensitivity OR Specificity



Diff 15%



Diff 20%



Diff 25%

[5% two-sided significance, Power 80%. Compare proportions with X^2 , $P < 0.05$, 95%CI]

Kit Analysis: Ideal

- 1. **Sensitivity & Specificity:** min. 75 pos. & 75 neg. including interfering substances or cross-reacting sera. Calculate delta values.
- 2. **Precision:** neg, low, medium, high pos. x 20 each
 - within run
 - between runs
 - between labs.
 - between batches
- 3. **Limit of detection:** 10 sera in dilution series
- 4. **Linearity for quantitative kits:** plot range 5 sera

Kit Analysis: Practical

- 1. **Sensitivity & Specificity:** 50 pos. & 50 neg. including 5 possible cross reactive sera. Calculate delta values.
- 2. **Precision:** one medium pos. x 10
 - within run
 - ~~between runs (later)~~
 - ~~between labs. (QAP)~~
 - ~~between batches (later)~~
- 3. **Limit of detection:** 1 or 2 sera in dilution series
- 4. **Linearity for quantitative kits:** plot range (later)

Kit Analysis: Reality

- Pilot study with one kit each
- Check literature & RCPA QAP reports
- Expand numbers after narrowing field

Measles IgG Kit Analysis: Reality?

12 manufacturers:

Bouty, Dade Behring, DiaSorin, Diesse, DSL, Equipar, Euroimmune, GenBio, PanBio, Trinity Biotech, Virion Serion, Vital Diagnostics.

Test 50 neg. & 100 pos = 2 kits each = 24 kits

Minimum volume = 300 ul each serum

Measles IgG kit pilot trials

pos = 50 neg = 41	Dade Behring	Vital	Euro- immune	Bouty	Equipar
Sensitivity (Pos agree)	100	98	98	100	49
Specificity (Neg agree)	100	100	100	67	63
Efficiency (Total agree)	100	99	99	84	40
δ negative	-6.70	-3.55	-5.71	-0.64	-0.66
δ positive	1.01	0.90	0.69	1.16	-0.76
CV	6%	4%	7%	4%	18%