Could a persistent cough be whooping cough?

Epidemiology and Statistics Module
Lecture 3

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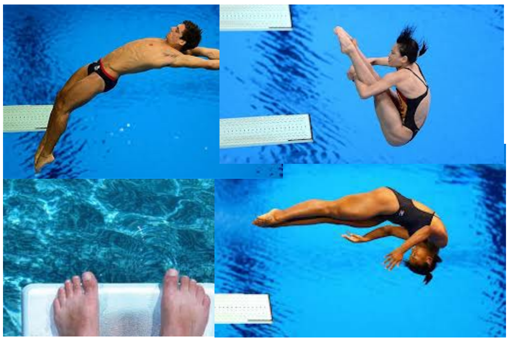

Aims of lecture

- To explain how to interpret a confidence interval
- To explain the different ways of comparing two proportions including odds ratios
- To explain P-values using the chi-squared test as an example
- To explain what survival curves are
- To describe the Erickson framework for assessing immunisation programmes
- To introduce methods for assessing diagnostic tests (more in the next lecture)

Harnden paper

"For school age children presenting to primary care with a cough lasting two weeks or more, a diagnosis of whooping cough should be considered even if the child has been immunised. Making a secure diagnosis of whooping cough may prevent inappropriate investigations and treatment."

Which figures in the paper support this conclusion?

A diagnosis of whooping cough should be considered……

64 children out of 172

64/172 x 100 = 37.2%

What is this?

Thought experiments:

What will happen if we take a different 172 children?
What will happen if we take lots of samples of 172?

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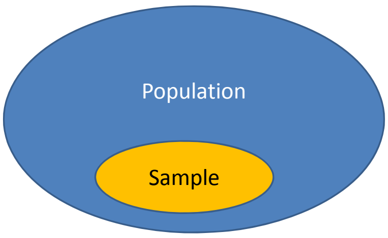
Inference

Trying to infer what might happen in the population from what happens in a sample



Do you ever infer from a sample to a population?

What assumptions do you make?

Confidence interval

Prevalence of whooping cough (amongst children aged 5-16 years who presented to their general practitioner with a cough lasting 14 days or more who consented to have a blood test)

= 64/172 x 100 = 37.2%

95% confidence interval 30.0% to 44.4%

Confidence interval interpretation

- We are 95% certain that in the population from which this sample is drawn the true percentage of individuals ***who have whooping cough*** is between 30.0% and 44.4%
- A measure of uncertainty – when you have a sample there is always some uncertainty
- Strictly can only be produced if your sample used random sampling of some sort

Amongst this cohort of students

True % of males? (I know this, you don't!)

Sample 1: 21, 1, 19, 7, 2, 17, 26, 9, 18, 26

% male =

Sample 2: 9, 22, 34, 5, 41, 25, 14, 15, 7, 17

% male =

....even if the child has been immunised

55 of the 64 (85.9%) fully immunised

No confidence interval given for this in the paper

Can we calculate one? (in the seminar)

Making comparisons

Look at those without whooping cough as well as those with whooping cough

Whooping cough

64 children
55 immunised
46/54 still coughing at 2 months

Not whooping cough

108 children
104 immunised
45/92 still coughing at 2 months

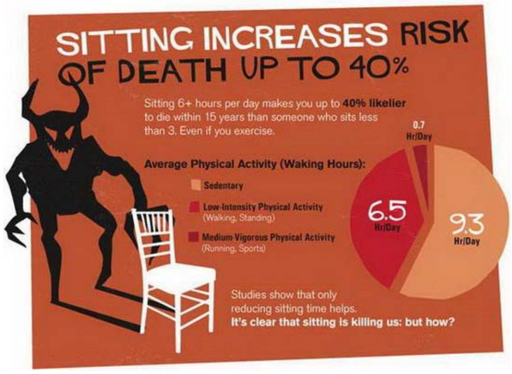
Comparing two proportions – often to compare the risk

1. The risk of mortality over the next 14 years is raised by 37% if you…….
2. 3 in a 1000 more individuals are likely to die in the next 14 years if they…..

Which risk would you prefer to take?

Calculated from relative risk (dividing one risk by another)

Calculated from absolute risk difference (subtracting one risk from another)



Two by two tables

	Whooping cough	Not whooping cough
Immunised	55	104
Not immunised	9	4

	Whooping cough	Not whooping cough
Coughing at 2 months		
Not coughing at 2 months		

Two by two tables

	Whooping cough	Not whooping cough
Immunised	55	104
Not immunised	9	4

	Whooping cough	Not whooping cough
Coughing at 2 months	46	45
Not coughing at 2 months	8	47

Two by two tables

	Whooping cough	Not whooping cough
Immunised	55	104
Not immunised	9	4

Looking backwards at what happened before whooping cough

	Whooping cough	Not whooping cough
Coughing at 2 months	46	45
Not coughing at 2 months	8	47

Looking forwards at what happens afterwards

Two by two tables

Starting point for different types of analyses

- Calculating proportions
- Calculating differences and relative risk
- Calculating odds ratios
- Is the difference between proportions likely to have arisen by chance?
- How good is a diagnostic test? (more next week)

Two by two tables – always put in totals

	Whooping cough	Not whooping cough	TOTALS
Immunised	55	104	159
Not immunised	9	4	13
TOTALS	64	108	172

Proportion of those with whooping cough who were immunised =55/64 = 85.9%

Two by two tables – always put in totals

	Whooping cough	Not whooping cough	TOTALS
Immunised	55	104	159
Not immunised	9	4	13
TOTALS	64	108	172

Proportion of those who have been immunised who get whooping cough = 55/159 = 34.6%

Proportion of those not immunised who get whooping cough = 9/13 = 69.2%

Is it worth being immunised?

- Relative risk(RR) of whooping cough if immunised
  = (55/159) / (9/13) = 34.6%/69.2% = 0.5 = 50%
- Relative risk reduction = 1 - RR = 50%
  The risk of whooping cough is decreased by 50% if a child is immunised
- Absolute risk difference (ARD) of whooping cough if immunised
  = (55/159) - (9/13) = -0.346 = -34.6% = 346 per 1000
  346 in 1000 fewer children get whooping cough if immunised

Maths note:

Fractions, proportions and percentages
Different ways of writing the same thing

41/100 = 0.41 = 41%
214/1000 = 0.214 = 21.4%
24/1000 = 0.024 = 2.4%
20/10000 = 2/1000 = 0.002 = 0.2%

Odds ratios (first calculate odds)

	Whooping cough	Not whooping cough	TOTALS
Immunised	55	104	159
Not immunised	9	4	13
TOTALS	64	108	172

Odds of getting whooping cough (wc)
= proportion with wc/proportion not having wc
= (55/159) / (104/159) = 55/104 for those immunised
= (9/13) /(4/13) = 9/4 for those not immunised

Odds ratios

	Whooping cough	Not whooping cough	TOTALS
Immunised	55	104	159
Not immunised	9	4	13
TOTALS	64	108	172

Odds ratio = ratio of two odds
= (55/104) / (9/4)
= (55 X 4) / (9 X 104)
= 0.23 = odds of getting whooping cough if immunised compared to not being immunised

Maths note:

(a/b) / (c/d) = $\frac{a/b}{c/d}$

= a/b X d/c

= (a X d) / (b X c)

If you don't believe this, try replacing a, b, c, d with some numbers.

This is fundamental to understanding the short cut to calculating odds ratios.

Ask your tutor in the seminar if you are still stuck.

Statistical significance tests

- Has this arisen by chance or is there some difference or some relationship in the data?
- Answered by a P-value but we have to know how to get there and what it means

Chi-squared test

	Whooping cough	Not whooping cough	TOTALS
Coughing at 2 months	46	45	91
Not coughing at 2 months	8	47	55
TOTALS	54	92	146

1. Numbers in white cells are observed values
2. Keep numbers in grey cells fixed

Chi-squared test – expected values

	Whooping cough	Not whooping cough	TOTALS
Coughing at 2 months	33.7	57.3	91
Not coughing at 2 months	20.3	34.7	55
TOTALS	54	92	146

62%

2. Keep numbers in grey cells fixed
3. Replace observed values with values expected if there is no difference between those with whooping cough and those without whooping cough
4. Make a judgement about whether the observed values are very different from those expected

Chi-squared test – observed values

	Whooping cough	Not whooping cough	TOTALS
Coughing at 2 months	46	45	91
Not coughing at 2 months	8	47	55
TOTALS	54	92	146

Probability

…….another word for ‘chance’

……..takes values between zero (no chance)

………and 1 (certain to happen)

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What's the chance of that happening?

- I unexpectedly met a work colleague at the theatre
- There was a kangaroo in my children's school playground
- My train was late this morning
- Getting the result that Harnden got if in reality the observed and expected values are the same, and the only reason for any difference is due to sampling

P-value

- The chance of getting this result if the in the whole population there is no difference (*ie the true observed values equal the expected values*)
- The chance of getting this result by chance
- In the case of the association between coughing at 2 months and whooping cough
- Perhaps surprisingly this indicates that this result is unlikely to have arisen by chance
- There is evidence that those who have whooping cough are more likely to be coughing at 2 months

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Differences in times

Instead of cough at 2 months, consider how long children coughed for altogether:

"However, the total duration of cough was greater for children with positive serology (median 112 days, range 38 to 191) than for those with negative serology (median 58 days, range 24 to 192)"

Why use medians and not means?

Difference in times
(Kaplan-Meier plots)

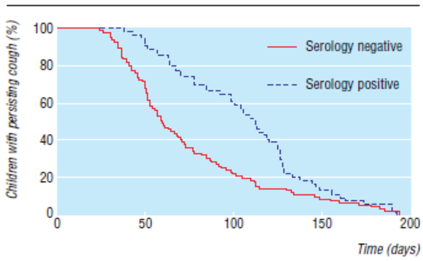

Fig 2 Proportion of children continuing to cough each day after onset, according to serology

Log rank test for comparison of survival curves

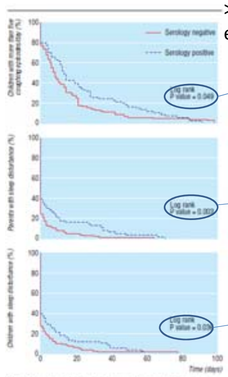

Fig 3 Proportion of children continuing to have more than five coughing episodes a day and proportions of parents and children with sleep disturbance

What do the P-values show?

P-values

By convention if $P<0.05$
- the difference is statistically significant at the 5% level
- we reject the hypothesis that there is no difference between the groups
- we have evidence that there is a difference

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P-values

Is there evidence that there are differences between those with and without whooping cough?

Yes!

- Coughing at 2 months 0.001
- More than 5 coughing episodes a day 0.049
- Parents with sleep disturbance 0.003
- Children with sleep disturbance 0.036

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Unadjusted and adjusted odds ratios (table in Harnden paper)

- Proportions vomiting
  - with whooping cough: 45/64
  - without whooping cough: 42/108
- Odds ratio (45 X 66) / (42 X 19) = 3.72
- Adjusted odds ratio = 4.35 (95% CI 2.04 to 9.25)
- *"Adjusted for age, sex, immunisation, asthma, parent smoking, household member coughing"*

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Issues that this paper raises….

Reliability of data
Effectiveness of immunisation
Effect of the research
Accuracy of diagnosis

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Reliability of data

- Recall bias from history taking
- Response bias from response rate
- More thinking about reliability in seminar

Questions about immunisation for whooping cough

- How effective is immunisation?
- Has immunisation changed?
- How many do not get immunised?
- Do those who are not immunised have worse symptoms?
- Is it worth immunising?
- Is there a systematic way of assessing immunisation programmes?

Assessing immunisation programmes - Erickson framework

1. Burden of disease
2. Vaccine characteristics
3. Immunisation strategy
4. Cost-effectiveness
5. Acceptability
6. Feasibility
7. Ability to evaluate
8. Research questions
9. Equity
10. Ethical considerations
11. Legal considerations
12. Conformity of programmes
13. Political considerations

HPV immunisation (human papillomavirus)

- For cervical cancer
- No evidence about prevention of deaths for a long time
- Used proxy outcomes to justify introduction

http://newsclick.in/india/paths-hpv-trials-india-troubling-questions

Trends

- What would you expect to happen as a result of the paper?
- Fewer vaccinations?
- Greater identification?
- How do we look at trends?
- Find out about trends and what has happened since the article from recent on-line articles in preparation for the seminar

How did they confirm that the children had whooping cough?

- Serology (blood test)
  - 100 ELISA units/ml IgG concentration used as cut-off point for a positive diagnosis
- What do we know about serology?
- How good is this for diagnosis?
- Are people ever misdiagnosed?
- What is the gold standard? (look in the module glossary for definition)
- What other situations can you think of where a blood test can be used to diagnose but is not a perfect diagnosis?

Diagnosing whooping cough amongst those with persistent cough

- Laboratory tests
  - Culture
  - PCR
  - Serology
- Symptoms
  - Paroxysmal cough
  - Vomiting
  - Whooping

(for more detail see Harnden, 2010)

Measures to judge how good a test is

- Specificity
- Sensitivity
- Positive predictive value
- Negative predictive value

(more on all of this next week- some covered in Harnden 2010 paper)

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Diagnosis using serology

Test says they do = 76%

Sensitivity

People who really **do** have whooping cough

Test says they don't = 99%

Specificity

People who really **don't** have whooping cough

Summary

- How to interpret a confidence interval
- Comparing proportions: relative risk, relative risk reduction, absolute risk difference, odds ratio
- P-values, chi-squared test and log-rank test
- Erickson framework for assessing immunisation programmes
- Diagnosis and gold standards, sensitivity and specificity

Seminar

- Routine data & reliability
- Looking at trends in whooping cough
- Calculating and understanding confidence intervals
- Calculating and understanding odds ratios

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Preparation for next week

Additional reading on whooping cough for seminar:

http://www.bbc.co.uk/news/health-16425519

Reading for next week's lecture on breast screening:

Article by Howard Wainer from 'Significance'

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