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Risk factor analysis

BS, DVM, PhD, DACVPM
Professor
Department of Production Animal Studies
University of Pretoria
Co-Editor-in-Chief for *Preventive Veterinary Medicine*

Geoffrey T. Fosgate

GF-TADs
Foot and Mouth Disease
Risk Assessment Training Workshop
Johannesburg, South Africa 19-21 September 2023

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Measures of association

- Epidemiology brief
- Association versus effect
- Measures of association
  - Risk difference
  - Vaccine efficacy
  - Risk ratio
  - Odds ratio
- Statistical significance
- Expert opinion exercise

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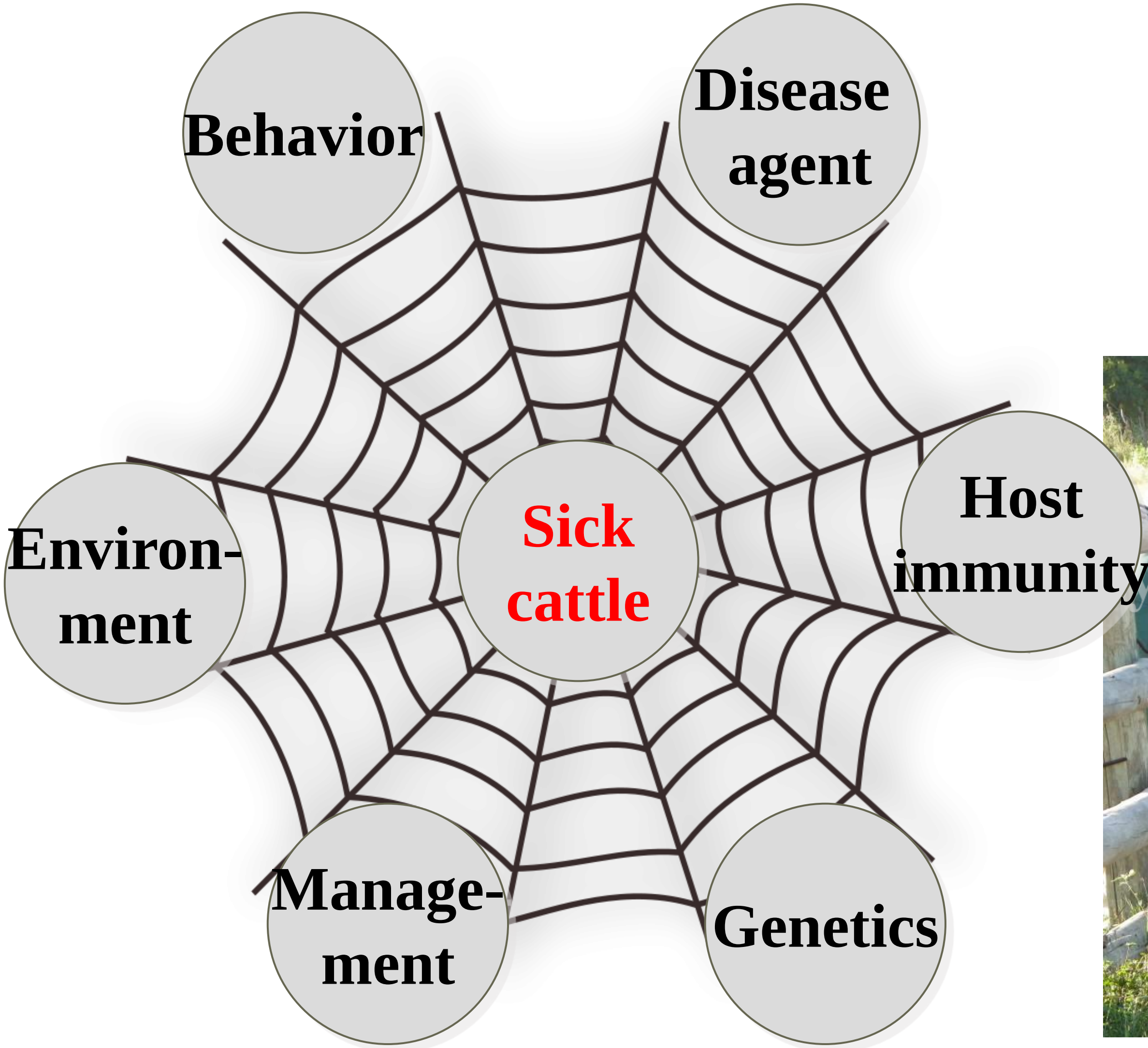
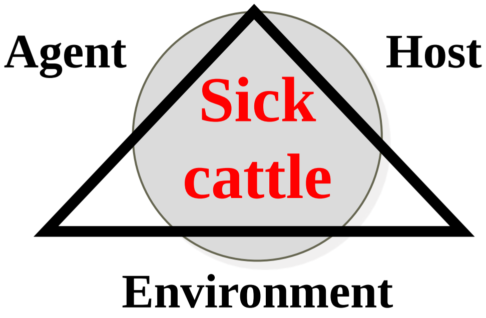
Epidemiology





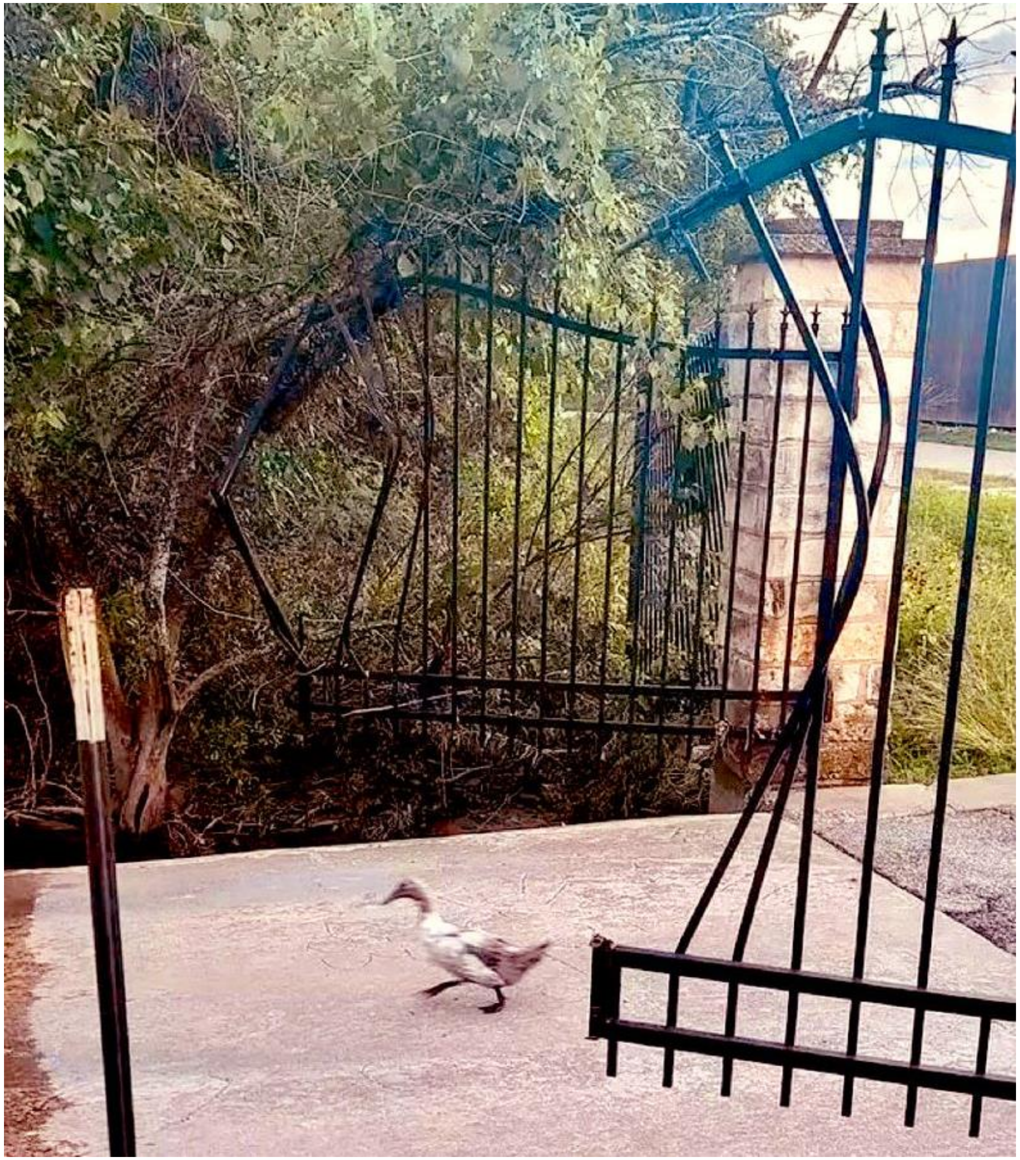
Purpose of epidemiology

- Determine the magnitude of disease in populations
- Study the natural history and prognosis related to disease
- Identify causes and predictors of health outcomes
- Evaluate preventive and therapeutic factors
- Collect quantitative data as the foundation for public policy

http://furballcottagenarrative.blogspot.com/

http://bojack.org/2006/05/breaking_news_bird_flu_outbrea.html

Correlation/causation



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Association/effect

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Publication of the International Union Against Cancer

DOES PIZZA PROTECT AGAINST CANCER?

Silvano GALLUS[1*], Cristina BOSETTI[1], Eva NEGRI[1], Renato TALAMINI[2], Maurizio MONTELLA[3], Ettore CONTI[4], Silvia FRANCESCHI[5] and Carlo LA VECCHIA[1,6]

[1]*Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy*
[2]*Centro di Riferimento Oncologico, Aviano (PN), Italy*
[3]*Istituto Tumori "Fondazione Pascale," Cappella dei Cangiani, Naples, Italy*
[4]*Istituto "Regina Elena" per lo Studio e la Cura dei Tumori, Rome, Italy*
[5]*International Agency for Research on Cancer, Lyon, France*
[6]*Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy*

We analyzed the potential role of pizza on cancer risk, using data from an integrated network of case-control studies conducted in Italy between 1991 and 2000. Cancer sites were: oral cavity and pharynx (598 cases), esophagus (304 cases), larynx (460 cases), colon (1,225 cases) and rectum (728 cases). Controls were 4,999 patients admitted for acute, non-neoplastic conditions to the same hospital network as cases. Odds ratios for regular pizza consumers were 0.66 (95% confidence interval, CI = 0.47–0.93) for oral and pharyngeal cancer, 0.41 (95% CI = 0.25–0.69) for oesophageal, 0.82 (95% CI = 0.56–1.19) for laryngeal, 0.74 (95% CI = 0.61–0.89) for colon and 0.93 (95% CI = 0.75–1.17) for rectal cancer. Pizza appears therefore to be a favorable indicator of risk for digestive tract neoplasms in this population.

Key words: *digestive tract cancers; lycopene; pizza; risk factors*

Pizza is one of the best known and most widespread Italian foods, and it is said to be the most common generic commercial sign of Italy worldwide. Investigating and quantifying any potential role of pizza on cancer risk seems to be a curious issue, but may well have interesting implications in respect to dietary advice in Italy as well as elsewhere.

Limited and inconclusive information is available on the potential influence of pizza, however, as a food item or as an indicator of any specific dietary pattern, on cancer risk. An inverse trend in risk with increasing number of portions of pizza was observed for prostate cancer in the U.S. Health Professionals Follow-Up Study.[1,2] In a case-control study from southern Italy on 132 cases of colorectal cancer, the odds ratio (OR) for frequent consumption of pizza was 0.89 (95% confidence interval, CI = 0.51–1.53).[3]

We analyzed data from a large and integrated network of case-control studies conducted in Italy, including detailed information on pizza eating as well as on a large number of potential confounding factors.

MATERIAL AND METHODS

Case-control studies on digestive tract and laryngeal neoplasms have been conducted between 1991 and 2000 in various regions of northern, central and southern Italy.[4–7] Our analysis included 598 patients (512 men, 86 women) with incident, histologically confirmed cancer of the oral cavity and pharynx, 304 (275 men, 29 women) with squamous-cell oesophageal cancer, 460 (415 men, 45 women) with cancer of the larynx, 1,225 (688 men, 537 women) of the colon and 728 (437 men, 291 women) of the rectum. The comparison group included 4,999 patients (2,724 men, 2,275 women) admitted to the same hospital network as cases for acute, non-neoplastic diseases. Twenty-five percent of controls were admitted for traumas, 30% for other non-traumatic orthopaedic conditions, 18% for acute surgical disorders and 27% for miscellaneous other illnesses. Response rate was more than 95% for both cases and controls.

All subjects were interviewed using a standard questionnaire, including information on socio-demographic factors and lifestyle habits, such as tobacco smoking and alcohol consumption. Subjects' usual diet before diagnosis (or hospital admission) was investigated using a validated 78-item food frequency questionnaire[8–9] that included a specific question on pizza. For the present analyses, pizza eating was classified in 3 categories: non eaters (<1 portion of pizza/month), occasional eaters (1–3 portions/month) and regular eaters (1 portion of pizza or more/week).

OR and the corresponding 95% CI, for subsequent levels of pizza eating were derived by unconditional multiple logistic regression models, including terms for age, gender, study center, education, alcohol and tobacco consumption, energy intake, body mass index and for colon and rectum, a measure of physical activity.

RESULTS

Table I shows the distribution of cases and controls according to pizza consumption and the corresponding multivariate ORs. Compared to non-pizza-consumers, the multivariate ORs for pizza eaters (≥1 portion/month) were 0.73 for oral cavity and pharynx, 0.53 for esophagus, 0.85 for larynx, 0.81 for colon and 0.88 for rectum. Corresponding ORs for regular pizza eaters (≥1 portion/week) were 0.66 for oral and pharyngeal, 0.41 for oesophageal, 0.82 for laryngeal, 0.74 for colon and 0.93 for rectal cancer. The trends in risk were significant for oral and pharyngeal, esophageal and colon cancers.

No appreciable difference was found according to gender for colorectal cancer, the ORs of pizza consumers being 0.78 (95% CI: 0.65–0.94) in men and 0.82 (95% CI: 0.66–1.02) in women for colon cancer, and 0.91 (95% CI: 0.73–1.14) and 0.82 (95% CI: 0.63–1.08) respectively for rectal cancer (not shown in Table I). The data were inadequate to analyze women only for upper digestive and respiratory tract neoplasms.

DISCUSSION

The findings of this uniquely large and integrated series of case-control studies from Italy suggest that pizza eating is a favorable indicator of risk for digestive tract neoplasms. In contrast, major sources of refined carbohydrates in Italy, mainly bread and pasta, were directly associated with the risk of colorectal

Grant sponsor: Italian Association for Cancer Research and the Italian League Against Cancer.

*Correspondence to: Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea, 62, 20157-Milan, Italy. Fax: +39-02 33200231. E-mail: gallus@marionegri.it

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Does pizza protect against cancer?
Silvano Gallus, Cristina Bosetti, Eva Negri, Renato Talamini, Maurizio Montella, Ettore Conti, Silvia Franceschi, Carlo La Vecchia
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Association/effect

Table I. Odds ratios (OR) and 95% confidence intervals (CI) for various Neoplasms[1] According to Pizza Consumption in Italy 1991–2000

Cancer	Pizza eaters			OR (95% CI)[2]			χ^2 trend (p)[4]
	Non	Occasional[3]	Regular[3]	Occasional[3]	Regular[3]	All eaters	
Oral cavity and pharynx	310	213	75	0.76 (0.60–0.95)	0.66 (0.47–0.93)	0.73 (0.59–0.91)	7.92 (0.005)
Oesophagus	175	105	24	0.57 (0.42–0.78)	0.41 (0.25–0.69)	0.53 (0.39–0.72)	17.46 (<0.001)
Larynx	236	167	57	0.86 (0.66–1.11)	0.82 (0.56–1.19)	0.85 (0.66–1.08)	1.71 (0.191)
Colon	503	473	249	0.84 (0.72–0.97)	0.74 (0.61–0.89)	0.81 (0.70–0.93)	10.97 (0.001)
Rectum	301	260	167	0.85 (0.71–1.02)	0.93 (0.75–1.17)	0.88 (0.74–1.04)	0.74 (0.390)
Controls	1,836	2,016	1,147	—	—	—	—

Association/effect

- Epidemiological studies measure associations
  - Mathematical relationship between two variables
  - Correlation between an exposure and disease
  - Correlation ≠ causation; only a small subset of correlated associations will be causal
- A causal relationship is when the change in one variable directly “effects” the results in another variable

- Epidemiology is used to study population-level effects and it is typically impossible to “look under the bed sheets” to see the causal mechanisms
- Data are imperfect and people interpret data based on preconceived beliefs
- If you start eating more pizza will your risk of cancer decrease?

Measures of association

- The strength of an association (magnitude) can indicate the relative likelihood of a true causal relationship
- A minimum of four pieces of data are required; these data are frequently entered into a 2x2 table for analysis
  - The number exposed that developed disease
  - The number exposed that did not develop disease
  - The number not exposed that developed disease
  - The number not exposed that did not develop disease
- Measures that can be calculated include
  - Risk difference (measure of "impact")
  - Risk ratio (RR)
  - Prevalence ratio (PR)
  - Odds ratio (OR)

Risk difference

- The difference of two risks (probabilities)
- Often referred to as the attributable risk (AR)
- Values range between -1 and 1 with 0 being the null value
- Calculated as: [a / (a+b)] - [c / (c+d)]
- Use only when the study design allows calculation of probabilities
- Interpreted as "how much of the total risk in the exposed group can be attributed to the exposure itself"
- A measure of impact rather than evidence for a causal association
- RD = (75/475) – (25/525) = 0.11

		Pancreatitis Yes	Pancreatitis No	
Overweight	Yes	75 (a)	400 (b)	475
	No	25 (c)	500 (d)	525
		100	900	1000

Vaccine efficacy

- The fraction (or percent) of disease in the unvaccinated group that could be prevented through vaccination

- $VE_{\%} = \dfrac{\text{(CI in unvaccinated – CI in vaccinated)}}{\text{CI in unvaccinated}}$

- Cumulative incidence (unvaccinated) = 3 / 5 = 0.6
- Cumulative incidence (vaccinated) = 1 / 9 = 0.11
- $VE_{\%}$ = (0.6 – 0.11) / 0.6 = 0.81 or 81% efficacious

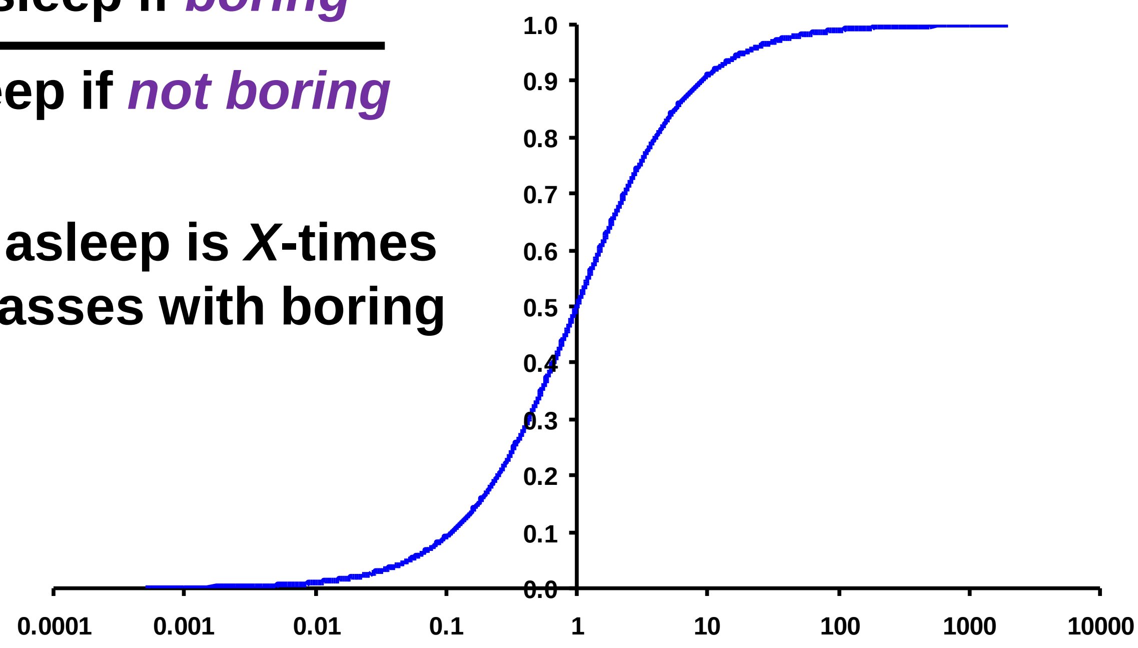
		FMD		
		Yes	No	
Vaccine	Exp +	1	8	9
	Exp -	3	2	5
		4	10	14

Risk ratio (RR)

- Also referred to as the relative risk (RR)
- The ratio of 2 risks (probabilities)
- Values range from 0 to infinity with 1 being the “null” value
- Range is asymmetric around 1
- Interpreted as “how many more times likely is it to fall asleep in class if the professor is boring?”

$$\frac{\text{Probability of falling asleep if } \textit{boring}}{\text{Probability of falling asleep if } \textit{not boring}}$$

- The probability of falling asleep is *X*-times greater for students in classes with boring professors



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Risk ratio (RR)

		Fell asleep: Yes	Fell asleep: No	
Boring Professor	Yes	25 (a)	35 (b)	60
	No	5 (c)	35 (d)	40
		30	70	100

- Calculated as: [a / (a+b)] / [c / (c+d)]
- Only use when the study design allows the calculation of probabilities
- Boring must be defined (and measured) independent of whether or not students fall asleep in class (!)
- RR = (25/60) / (5/40) = 3.33

Prevalence ratio (PR)

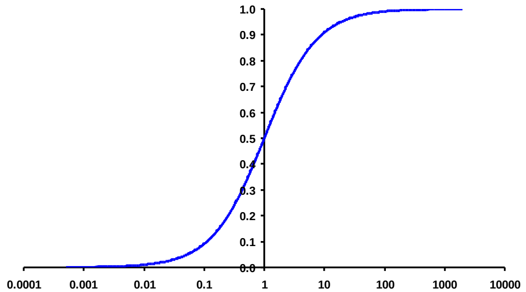
		Pajamas Yes	Pajamas No	
Boring Professor	Yes	25 (a)	35 (b)	60
	No	5 (c)	35 (d)	40
		30	70	100

- Calculated the same as the RR: [a / (a+b)] / [c / (c+d)]
- Appropriate for analysis of data from cross-sectional studies
- Interpretation: "The prevalence of pajama-wearing students is *X*-times higher in the class of a boring professor"
- Prevalence is a proportion but ***not*** a probability

Odds ratio (OR)

- The ratio of 2 odds
- Values range from 0 to infinity with 1 being the “null” value
- Range is asymmetric around 1
- Interpreted as “how many more times likely is it to fall asleep in class if the professor is boring?”

$$\frac{\text{Odds of falling asleep if } \textit{boring}}{\text{Odds of falling asleep if } \textit{not boring}}$$



- The odds of falling asleep are *X*-times greater for students in classes with boring professors
- Measure of association for case-control studies because it’s not possible to estimate risks directly from such studies

Odds ratio (OR)

http://i2.cdn.turner.com/cnn/dam/assets/120815025533-dull-and-boring-story-top.jpg

Fell asleep

		Case	Control	
Boring	Yes	40 (a)	20 (b)	60
Professor	No	10 (c)	30 (d)	40
		50	50	100

- Calculated as: [a/b] / [c/d]; [a/c] / [b/d] -or- [a*d] / [c*b]
- When the outcome is rare in the source population (rule of thumb is 5% or less) then is a good approximation for the risk ratio

  a / (a + b) ≈ a / b when *a* is small relative to *b* (in source population)

  c / (c + d) ≈ c / d when *c* is small relative to *d*
- The OR is mathematically the same irrespective of how it is calculated and only the theoretical interpretation varies

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P value

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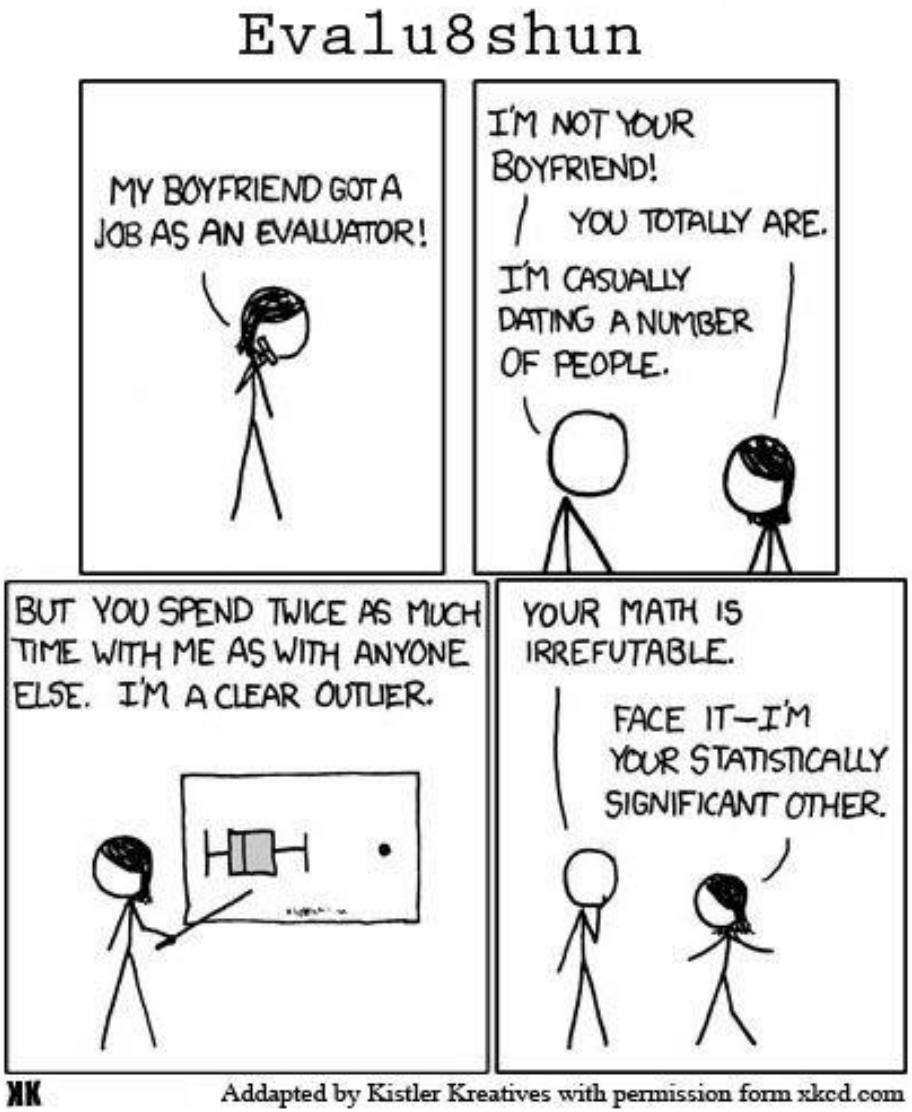
Significant associations



https://za.pinterest.com/pin/189291990559151462/

- A P-value is the probability of observing the current data, or more extreme, when there is no association
- P-values that are large are consistent with “no association” or no effect
- Small P-values suggest a true association and are considered “significant” when $P < 0.05$
- The purpose is to provide an objective criterion that does not vary from individual to individual

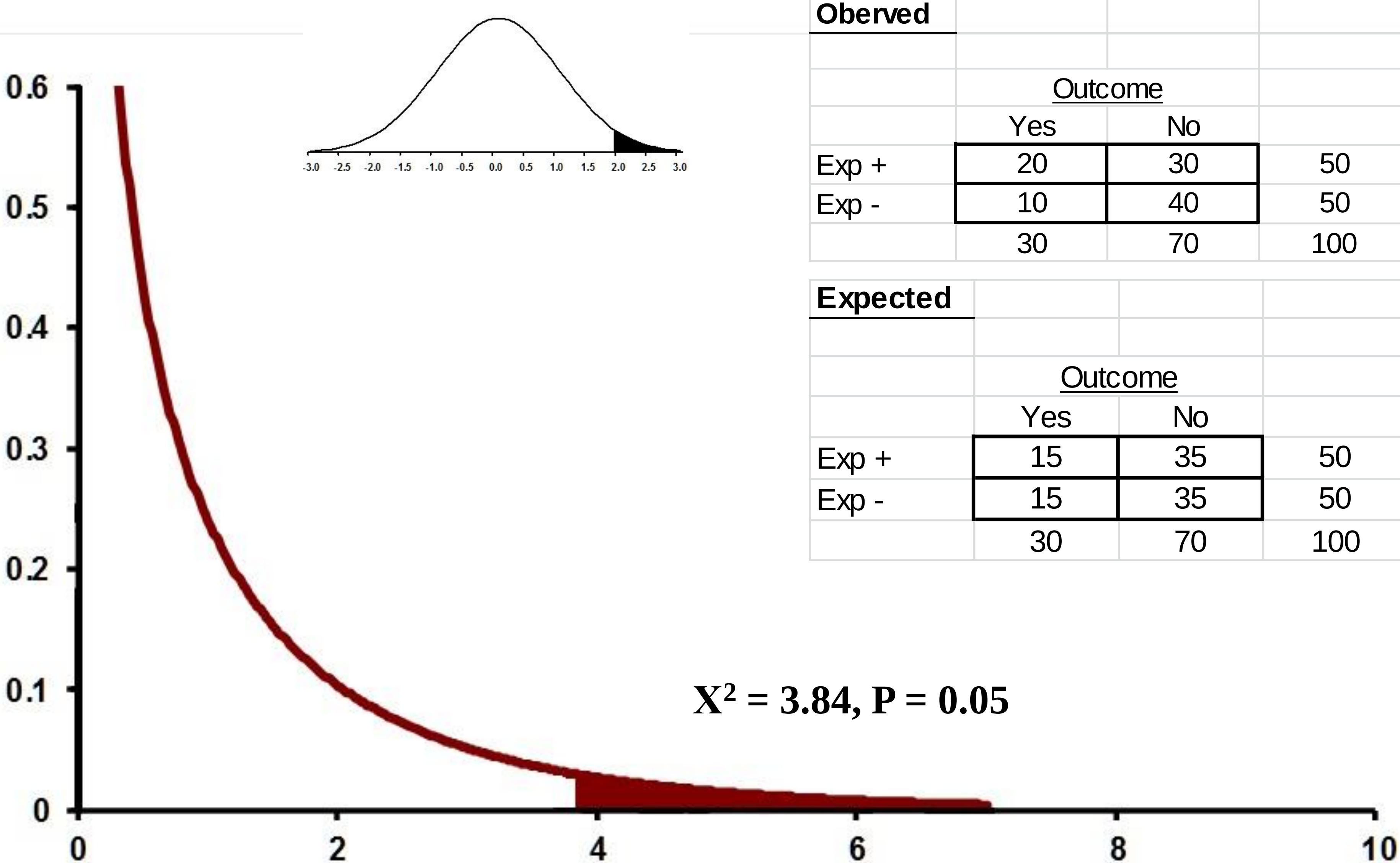
Chi-square distribution

Oberved

	Outcome		
	Yes	No	
Exp +	20	30	50
Exp -	10	40	50
	30	70	100

Expected

	Outcome		
	Yes	No	
Exp +	15	35	50
Exp -	15	35	50
	30	70	100



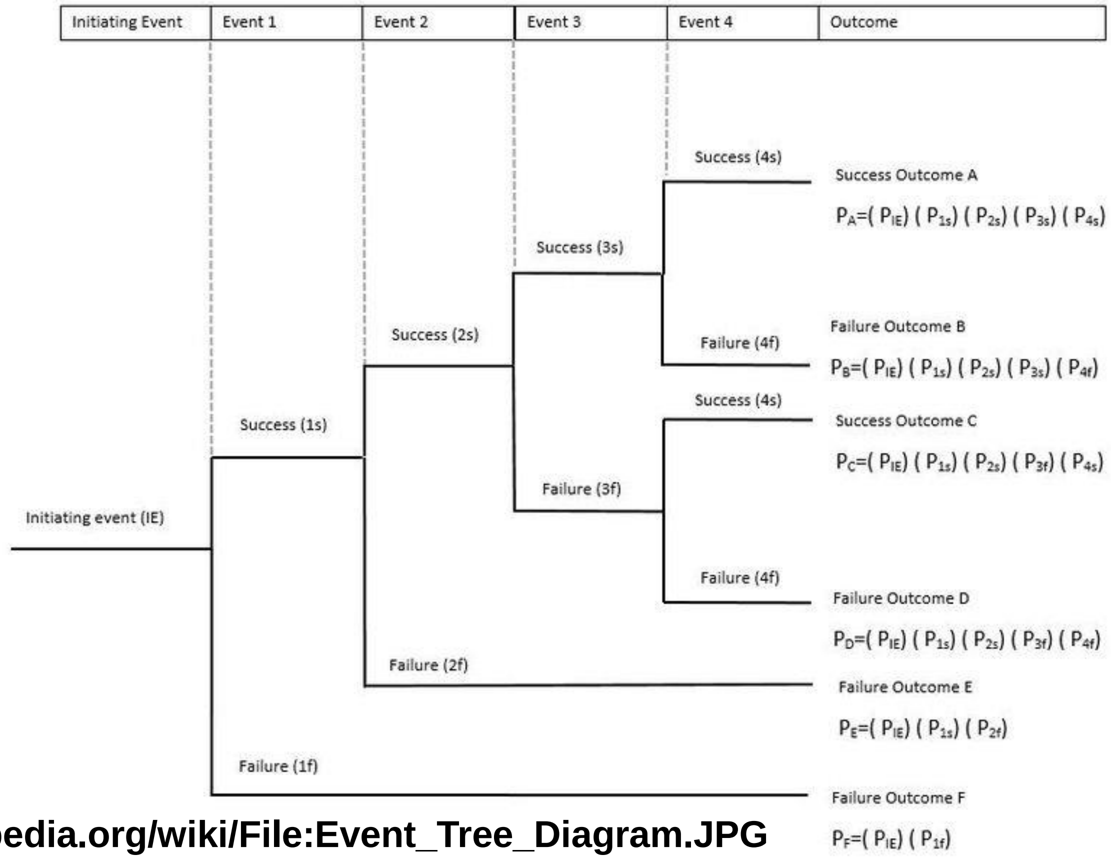
$X^2 = 3.84$, $P = 0.05$

Expert opinion elicitation

- Epidemiological studies collect data to estimate effects and risks of disease
- Data are often not available when performing risk assessments
- Probabilities therefore cannot be estimated directly and must be generated from expert opinion
- Can be generated via:
  - Delphi method – a process used to arrive at a group opinion or decision by surveying a panel of experts. Experts respond to several rounds of questionnaires, and the responses are aggregated and shared with the group after each round.
  - Personal interview
  - On-line, mail questionnaire
  - Extraction and summarization of information from the literature – meta-analysis
- Should account for uncertainty by modelling using distributions

Quantitative assessment

- **Mathematical structure of the problem must be defined**
- **All inputs must be quantified**
  - **Fixed**
  - **Stochastic**
- **Statement of the acceptable level of risk**
  - **An example might be a probability of less than 1 in a million**
  - **Can be based on extrapolation from laboratory studies**

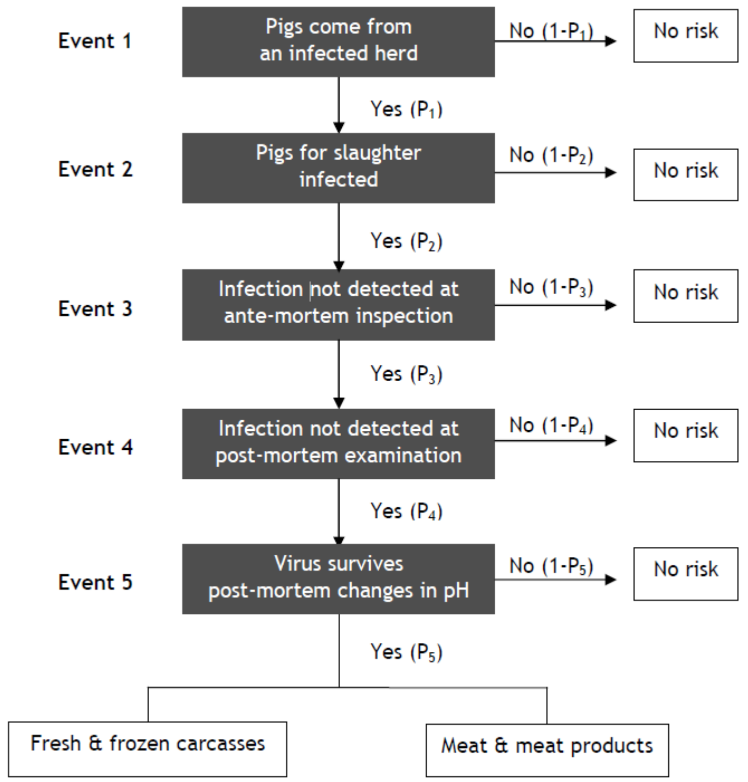


http://en.wikipedia.org/wiki/File:Event_Tree_Diagram.JPG

Quantitative assessment

- Mathematical structure of the problem must be defined
- All inputs must be quantified
  - Fixed
  - Stochastic
- Statement of the acceptable level of risk
  - An example might be a probability of less than 1 in a million
  - Can be based on extrapolation from laboratory studies

FIG 1: Scenario pathway for the risk of contaminating pork with FMD virus

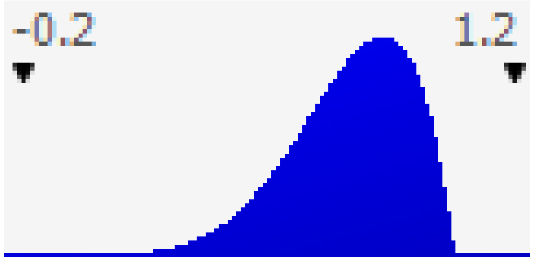


Risk assessment on Foot-and-Mouth Disease (FMD) in pork from vaccinated animals
E. LOPEZ, A. DEKKER, M. NIELEN

Expert opinion

- **Amount of virus in affected muscle**
- **The pH drop that is expected to occur in FMD microlesions relative to the surrounding muscle mass (eg. 50% drop would be pH = 6 if the rest of the muscle dropped to pH = 5)**
- **Mass of affected muscle tissue in each individual lesion**
- **Number of lesions per affected carcass**
- **Probability that an infected animal will develop such lesions**

- **Best guess:**
- **95% sure that it is less than:**
- **95% sure that it is greater than:**



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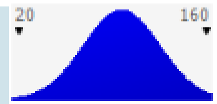
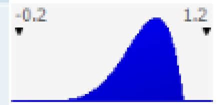
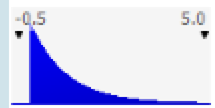
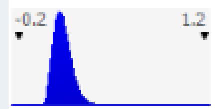
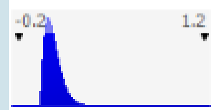
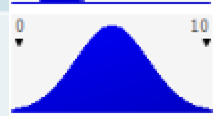
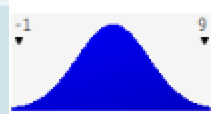
Modeling uncertainty

Input	Function	Density	Mean	Minimum	Maximum
Number of cattle within quarantine per cycle	Normal(147,26.6)		96.8	-∞	+∞
Biosecurity at quarantine station (camps, double fence)	Beta(5.3,2)		0.73	0	1
Basic reproductive number for subclinical cattle	Exponential(1)		1	0	+∞
Effect of ante and post-mortem inspection	Beta(5.6,30)		0.16	0	1
Trimmings (probability of LN)	Beta(2.3, 23)		0.09	0	1
Concentration of FMDV (PFU/g) in LN	Normal(5, 1.8)		5.0	-∞	+∞
Dose/infection constant; 'r'	Normal(4.1,1.8)		4.1	-∞	+∞

Expert opinion elicitation

	Cattle population	Proximity to a game reserve	Human population	Proximity to a road network	Proximity to rivers	Vaccine matching	Vaccination coverage	Vaccination interval	Cattle inspection	Permitted cattle movement into a village/location	Permitted cattle movement outside a village/location
Cattle population											
Proximity to a game reserve											
Human population											
Proximity to a road network											
Proximity to rivers											
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Vaccination coverage											
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Cattle inspection											
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Expert opinion elicitation

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Permitted cattle movement into a village/location											
Permitted cattle movement outside a village/location											

More Important				Equivalent	Less Important			
Extremley	Very Strongly	Strongly	Moderately		Moderately	Strongly	Very Strongly	Extremley
16 : 1	8 : 1	4 : 1	2 : 1	1 : 1	1 : 2	1 : 4	1 : 8	1 : 16

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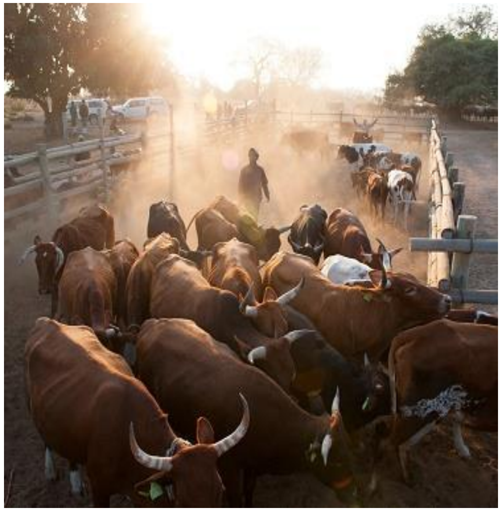
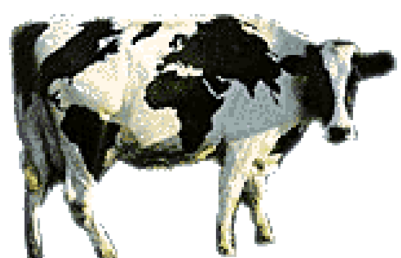


Thank you



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