Measures of Association II

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Lecture 6

Observed case numbers

Arverse outcome	*Treatment* NO	PO	PAR	$\sum$
yes	6	6	8	20
no	4	13	58	75
$\sum$	10	19	66	95

Lakos and Solymosi (2010)

Observed case numbers

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$\sum$	10	19	66	95

Expected case numbers

Arverse outcome	*Treatment* NO	PO	PAR	$\sum$
yes	2.11	4	13.89	20
no	7.89	15	52.11	75
$\sum$	10	19	66	95

Observed case numbers

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yes	6	6	8	20
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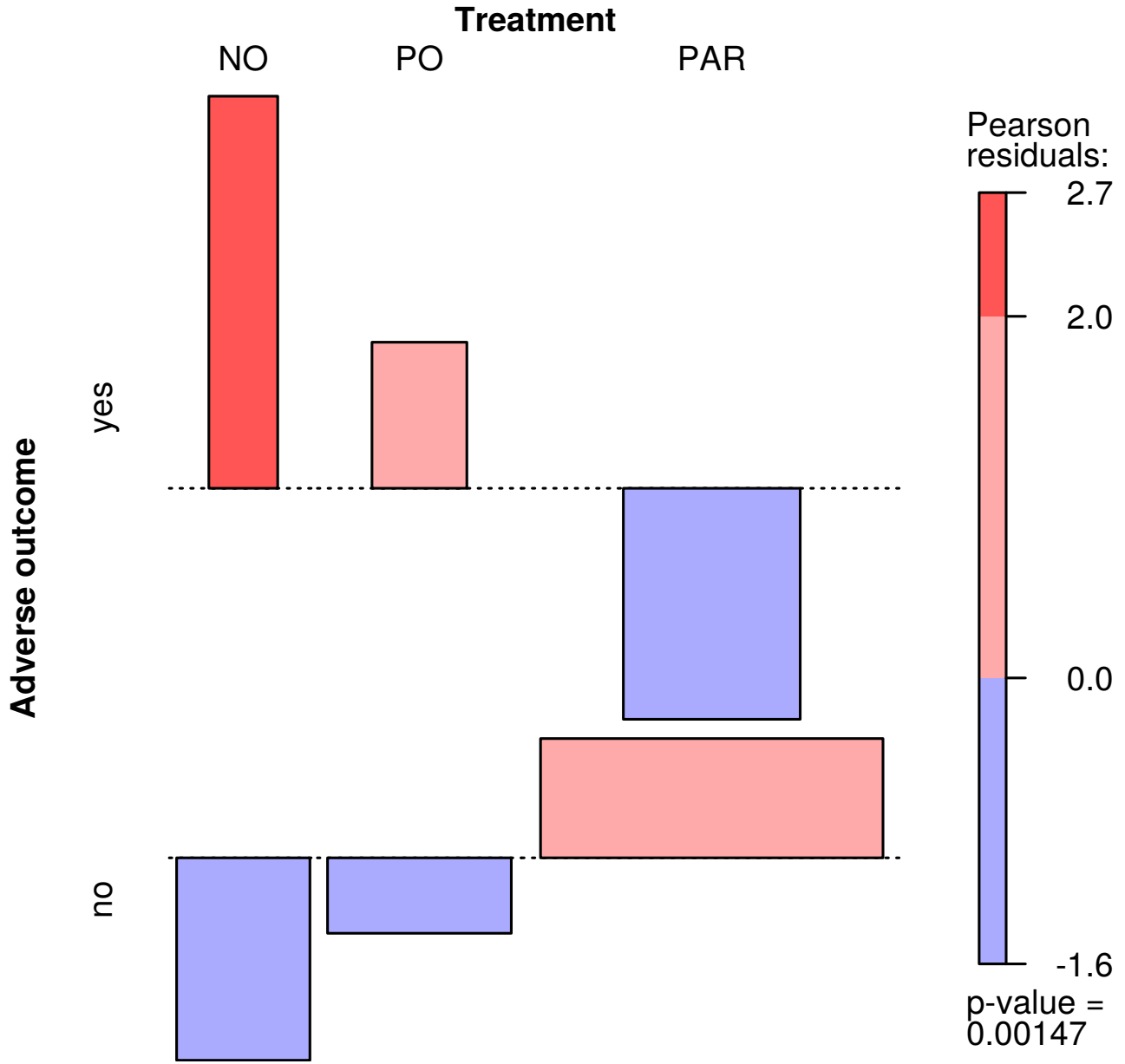
Expected case numbers

Arverse outcome	*Treatment* NO	PO	PAR	$\sum$
yes	2.11	4	13.89	20
no	7.89	15	52.11	75
$\sum$	10	19	66	95

Pearsons's **residuals**

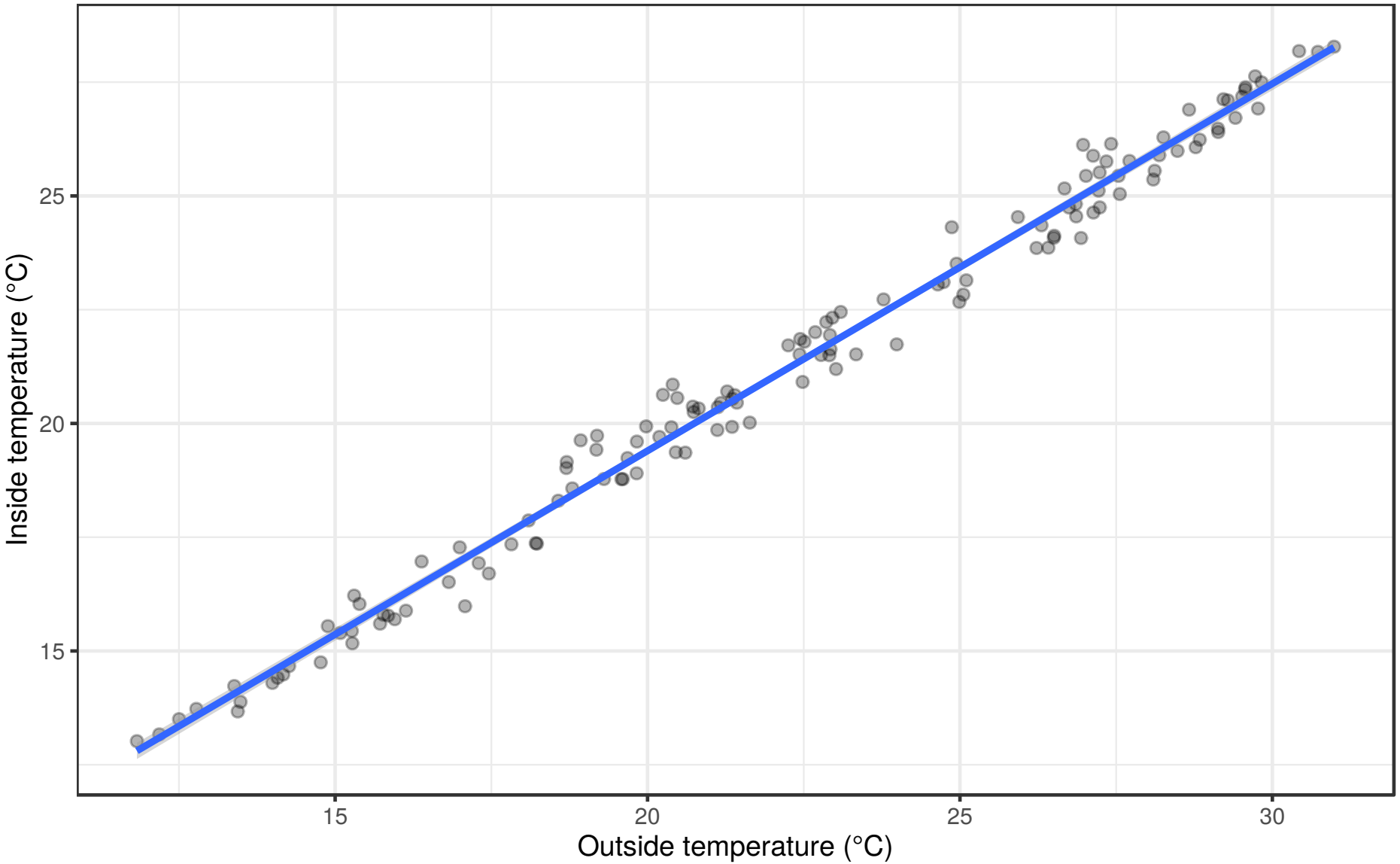
Arverse outcome	*Treatment* NO	PO	PAR
yes	2.68	1.00	-1.58
no	-1.38	-0.52	0.82

$$r_{ij} = \frac{o_{ij} - e_{ij}}{\sqrt{e_{ij}}}$$



Lakos and Solymosi (2010)

Temperature measured in parallel inside and outside the stable



What is the relationship between outside and inside temperature?

- correlation: $R = 0.9938484$

How depends the inside temperature on outside temperature?

- linear regression

```
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 3.261357   0.177733   18.35   <2e-16 ***
T.o         0.806852   0.007796  103.49   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.4621 on 133 degrees of freedom
Multiple R-squared:  0.9877,        Adjusted R-squared:  0.9876
F-statistic: 1.071e+04 on 1 and 133 DF,  p-value: < 2.2e-16
```

- $\beta = 0.806852$, means the inner temperature increases with ~ 0.81°C by 1°C increase of outer temperature

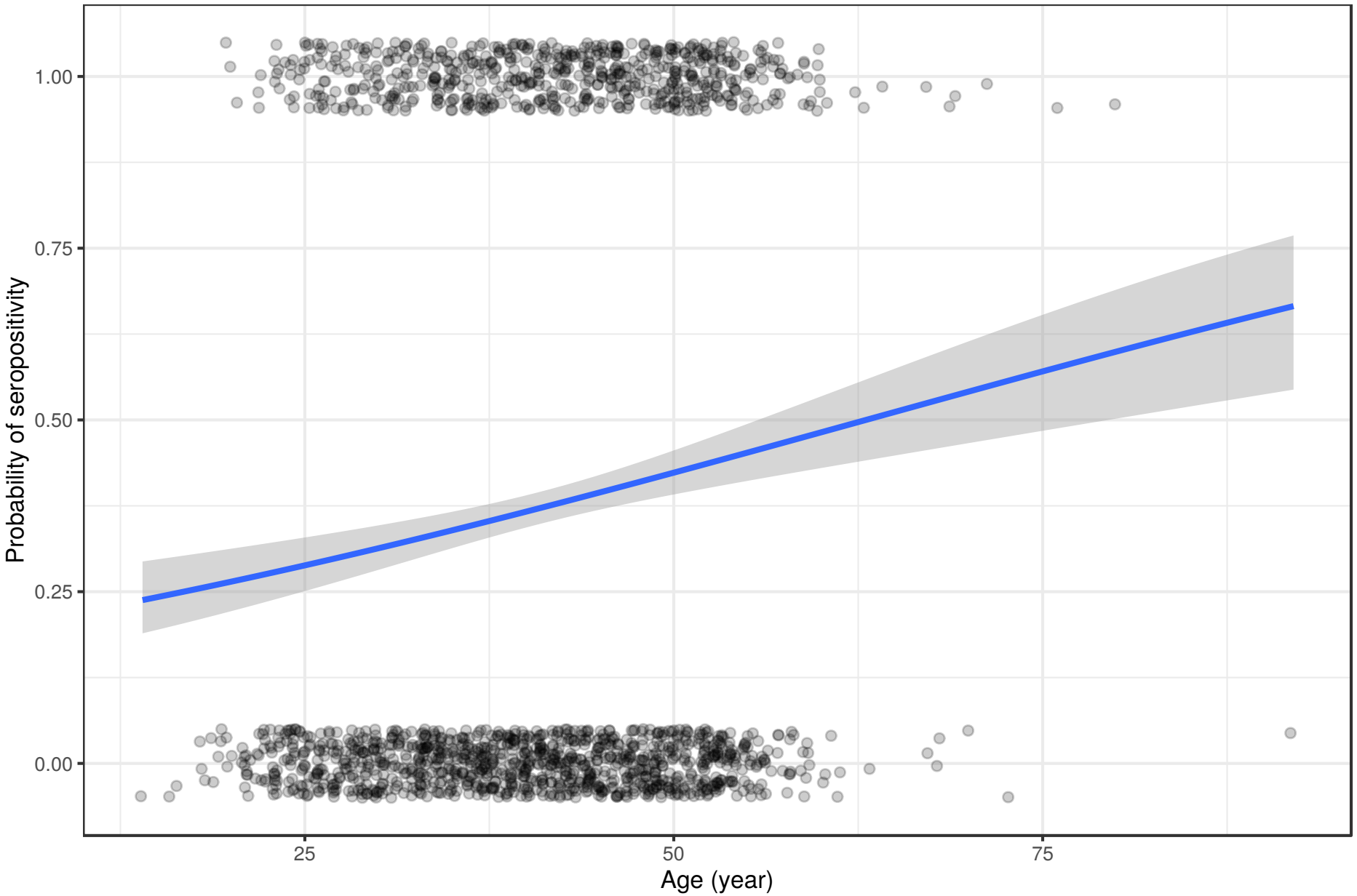
```
dat = rbind(
tibble(adverse.out=c(rep(1,6), rep(0,4)), AB='no'),
tibble(adverse.out=c(rep(1,6), rep(0,13)), AB='po')
) %>% mutate(AB=relevel(factor(AB), 'po'))

fit = glm(adverse.out ~ AB, family=binomial(link='logit'),
data=dat)
summary(fit)
```

```
Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -0.7732     0.4935  -1.567    0.117
ABno          1.1787     0.8126   1.451    0.147
```

```
round(exp(cbind(OR=coef(fit), confint(fit))),2)
```

```
               OR 2.5 % 97.5 %
(Intercept) 0.46   0.16    1.17
ABno        3.25   0.68   17.35
```

Lakos and Solymosi (2010)



Lakos et al. (2012)

```
   seropos   age
 1       0    33
 2       1    41
 3       1    50
 4       1    50
 5       0    55
```

```
fit = glm(seropos ~ age, family = binomial(link="logit"),
data=dat)
summary(fit)
```

```
Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.497757   0.215261  -6.958 3.45e-12 ***
age          0.023765   0.005055   4.701 2.59e-06 ***
```

```
round(exp(cbind(OR=coef(fit), confint(fit))),2)
```

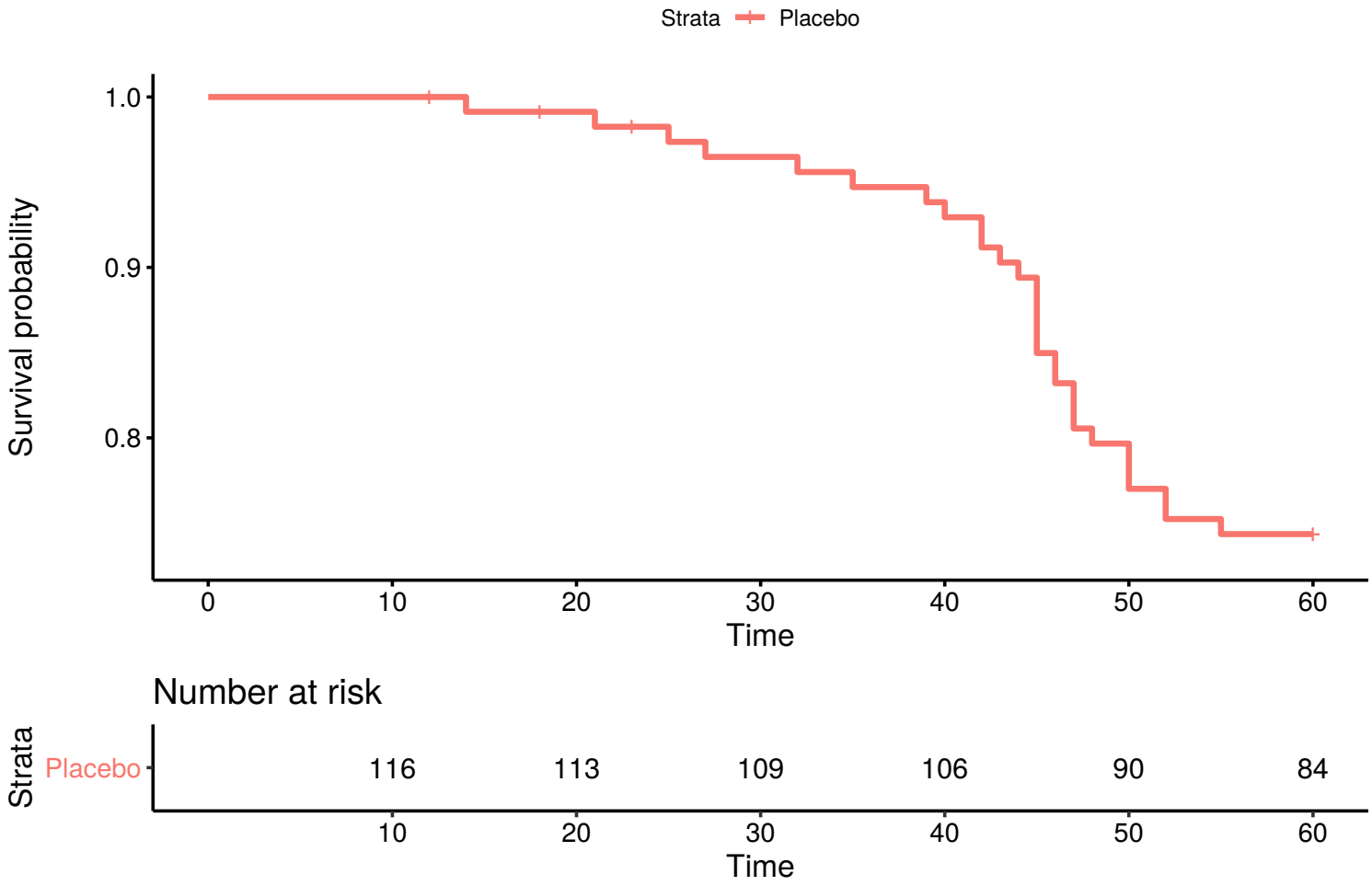
```
              OR 2.5 % 97.5 %
(Intercept) 0.22  0.15   0.34
age         1.02  1.01   1.03
```

Reference	Level	β	OR	CI	p
Male	Female	0.11	1.116	1.1–1.132	0.0000
Non-white	White	−0.011	0.989	0.971–1.008	0.2643
45–65	<45	0.376	1.456	1.404–1.509	0.0000
	65–80	−0.208	0.813	0.799–0.827	0.0000
	>80	−0.272	0.762	0.746–0.777	0.0000
1998–2003	2004–2009	0.835	2.304	2.27–2.338	0.0000
Poverty Q1	Q2	−0.042	0.959	0.94–0.978	0.0000
	Q3	−0.178	0.837	0.822–0.852	0.0000
	Q4	−0.254	0.775	0.758–0.793	0.0000
Colon	Esophagus	−1.015	0.362	0.349–0.377	0.0000
	Pancreas	−1.175	0.309	0.297–0.322	0.0000
	Rectum	−0.563	0.569	0.557–0.582	0.0000
	Small bowel	−1.466	0.231	0.219–0.244	0.0000
	Stomach	−0.928	0.395	0.383–0.409	0.0000

Lymph node retrieval during surgery for GI cancer remains inadequate in a large proportion of patients in the USA, although the median number of resected nodes increased over the last 10 years. Gender and socioeconomic disparities in receiving adequate lymphadenectomy were observed.

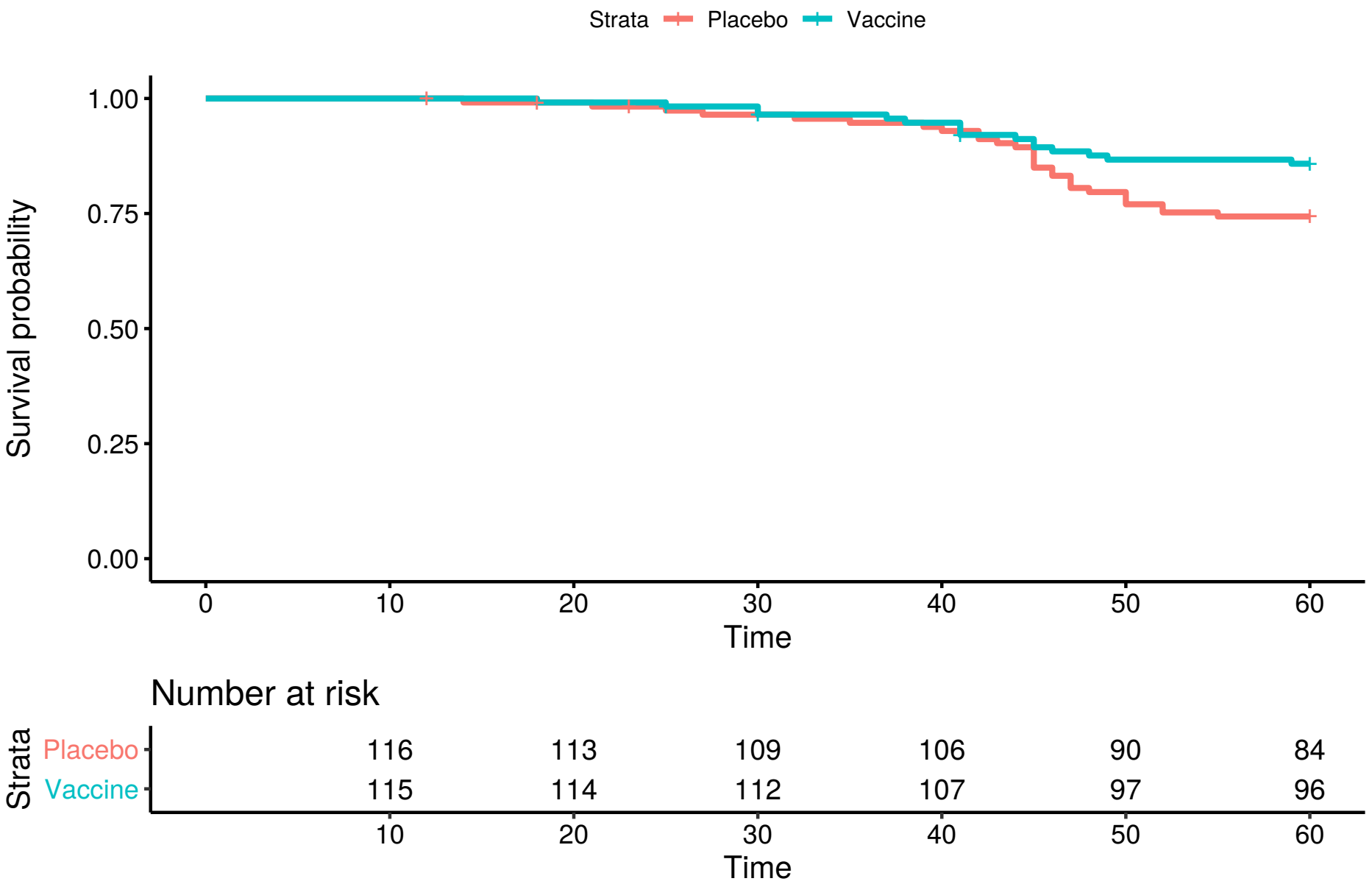
Dubecz et al. (2013)

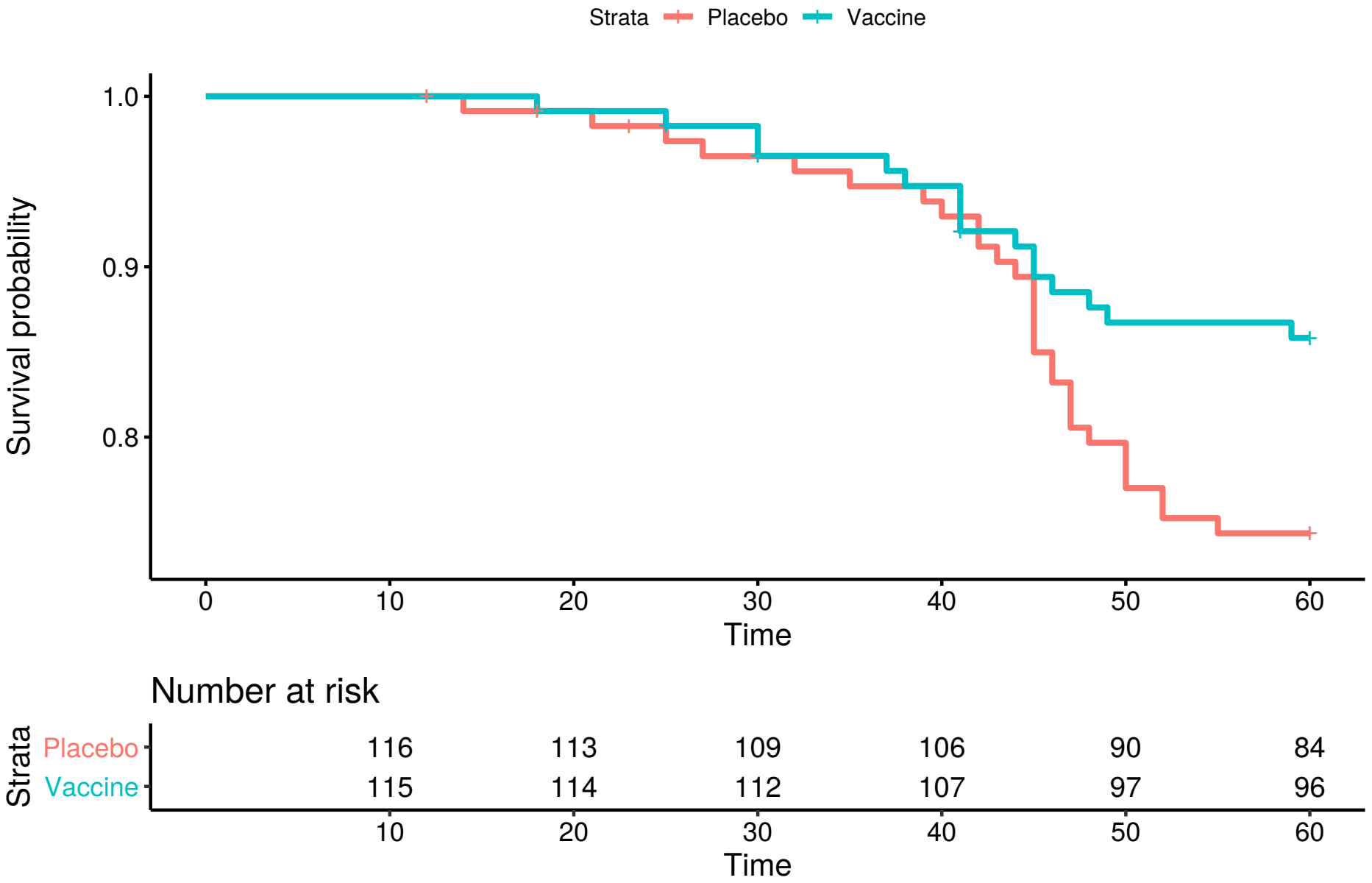
- vaccination trial in livestock production
- there were two groups (vaccinated and placebo) of about 115 animals
- the event was the diagnosis of clinical respiratory tract problems



Noordhuizen et al. (2001)

Test of difference by log-rank test, $p = 0.038$




Strata
Placebo
Vaccine
1.0
0.9
0.8
Survival probability
0
10
20
30
40
50
60
Time
Number at risk
Strata
Placebo
Vaccine
116
113
109
106
90
84
115
114
112
107
97
96
10
20
30
40
50
60
Time

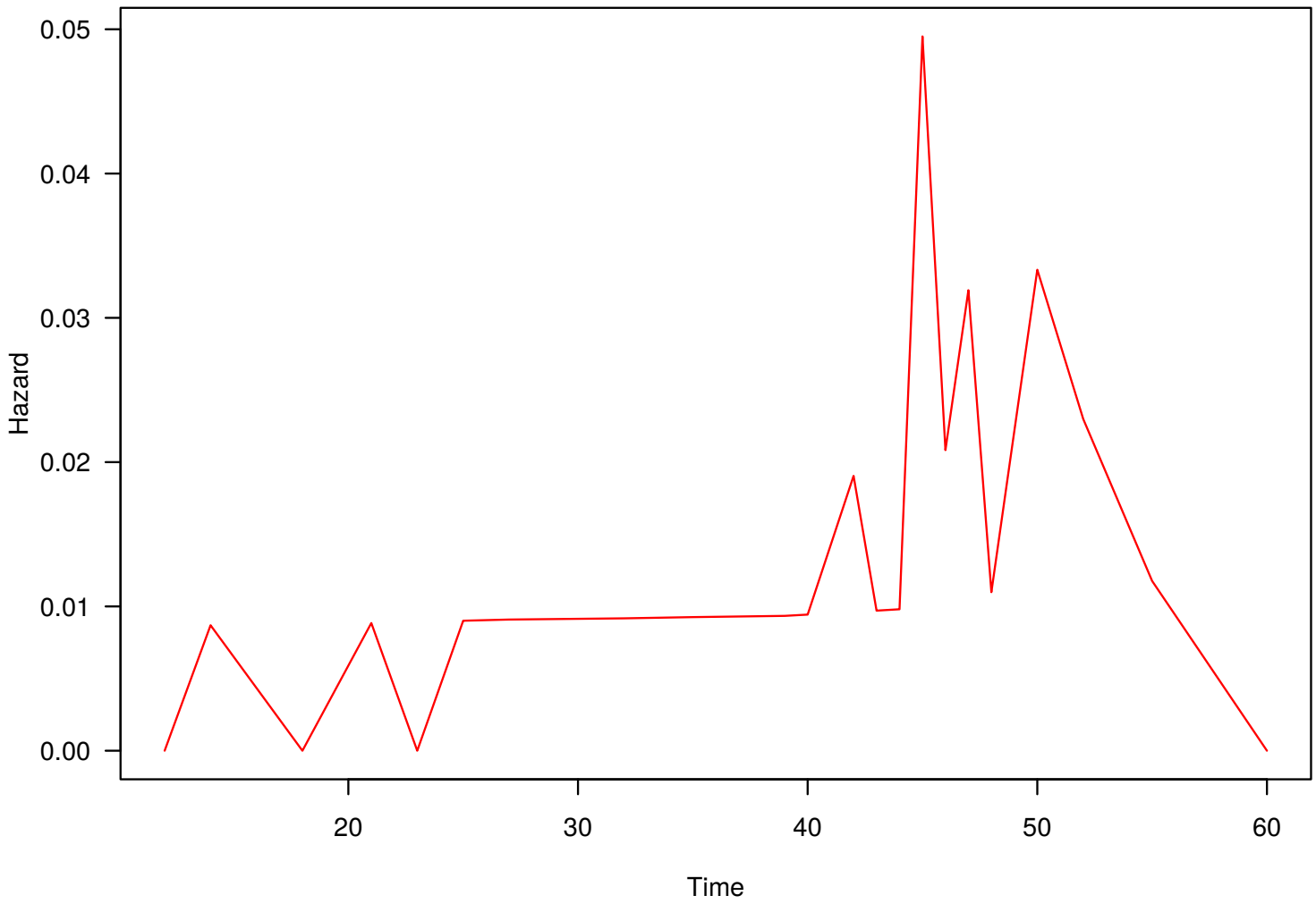
The hazard function $h(t)$* gives the probability that the event will occur in the next period of time, given that the individual has not yet shown the event

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t)}{\Delta t}$$

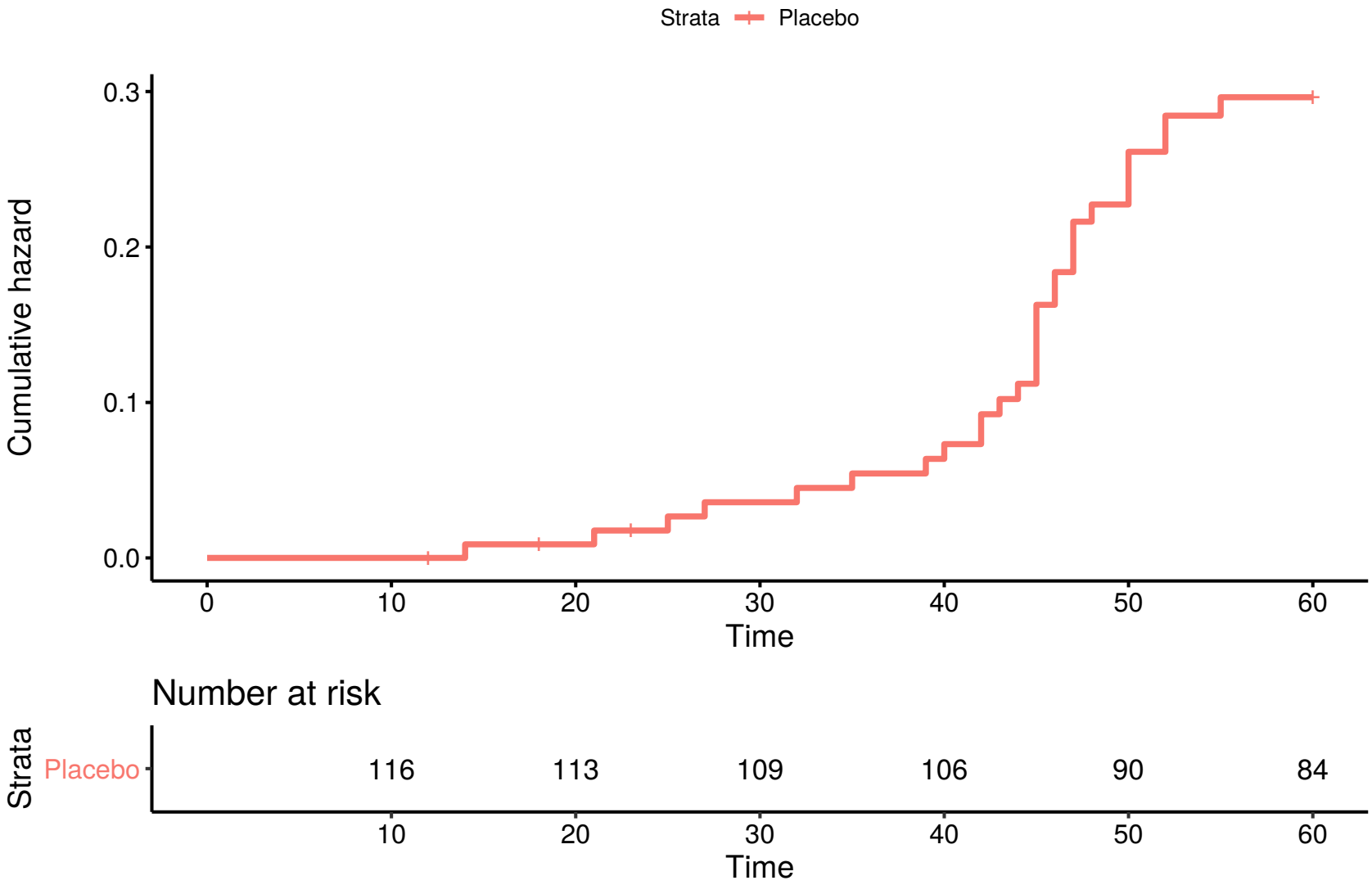
conditional probability:

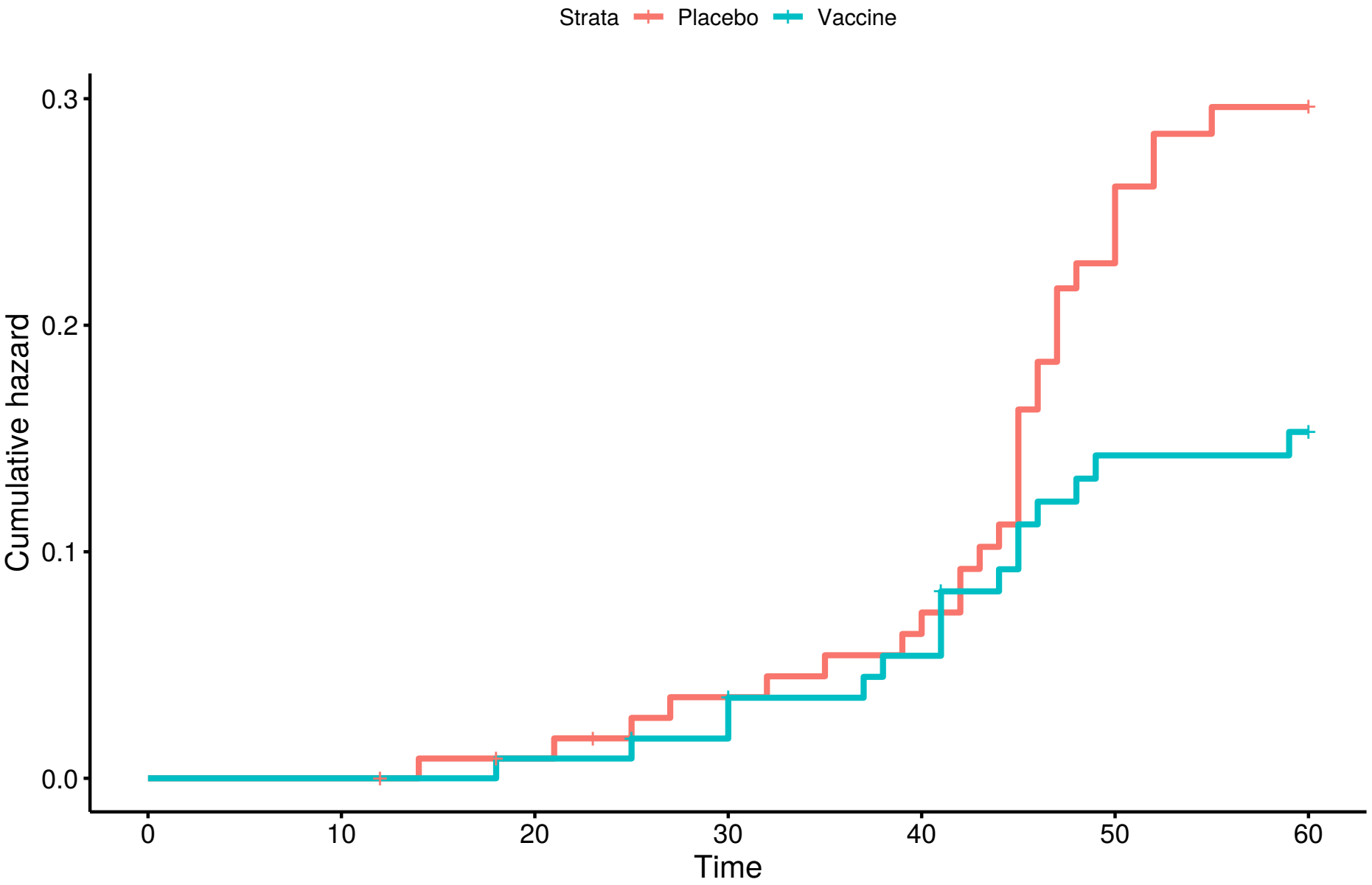
- let's say the probability of dying in the 80th year of life is 1% at birth%
- the same probability when someone is in the 79th year of life is higher, let's say 5%

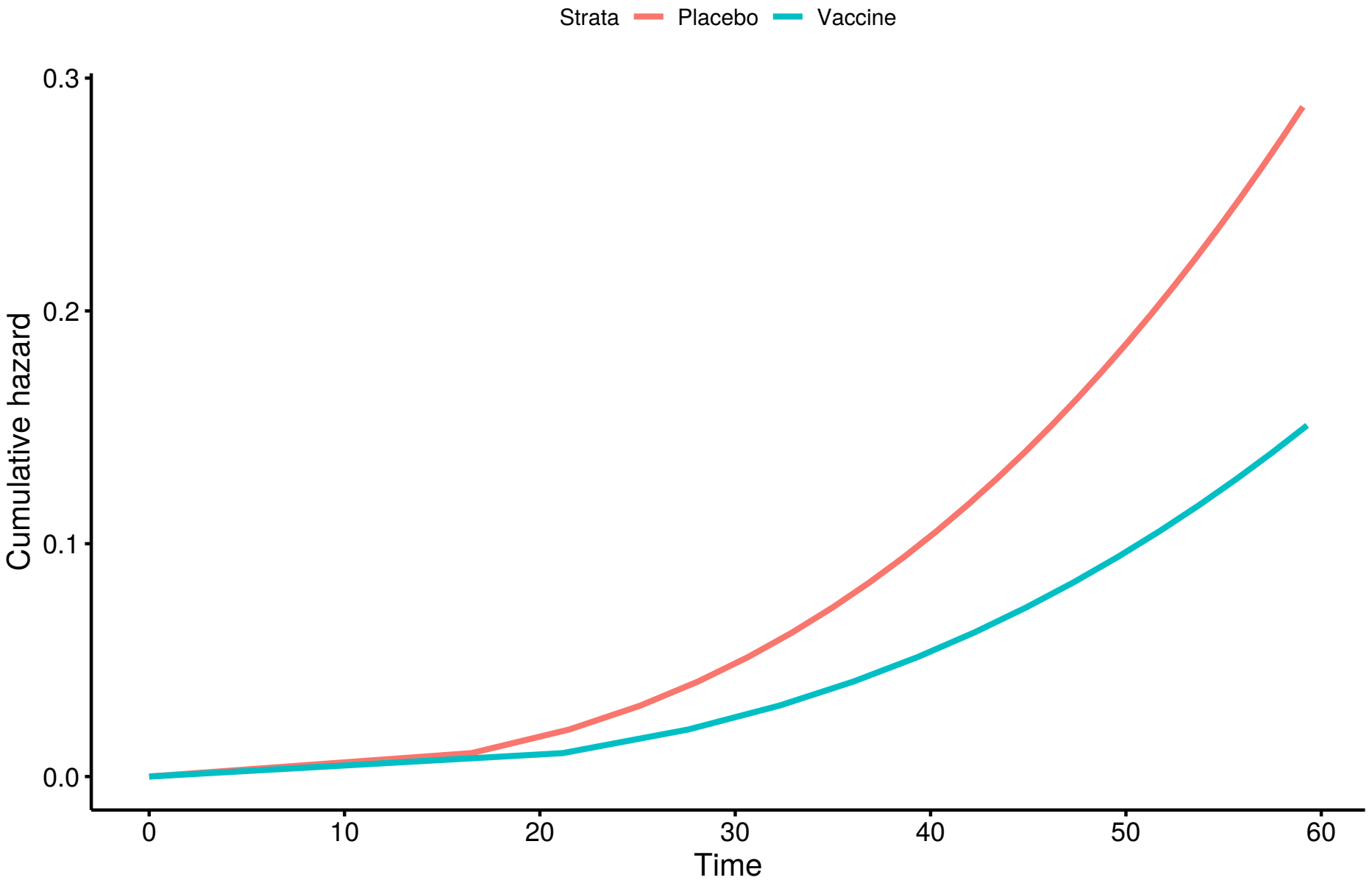
*hazard function



Since the hazard function shows significant variation per time unit, it is not used for plotting, but rather the cumulative hazard


Strata
Placebo
Cumulative hazard
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
Time
Number at risk
Strata
Placebo
116
113
109
106
90
84
10
20
30
40
50
60
Time


Strata
Placebo
Vaccine
Cumulative hazard
0.0
0.1
0.2
0.3
0
10
20
30
40
50
60
Time

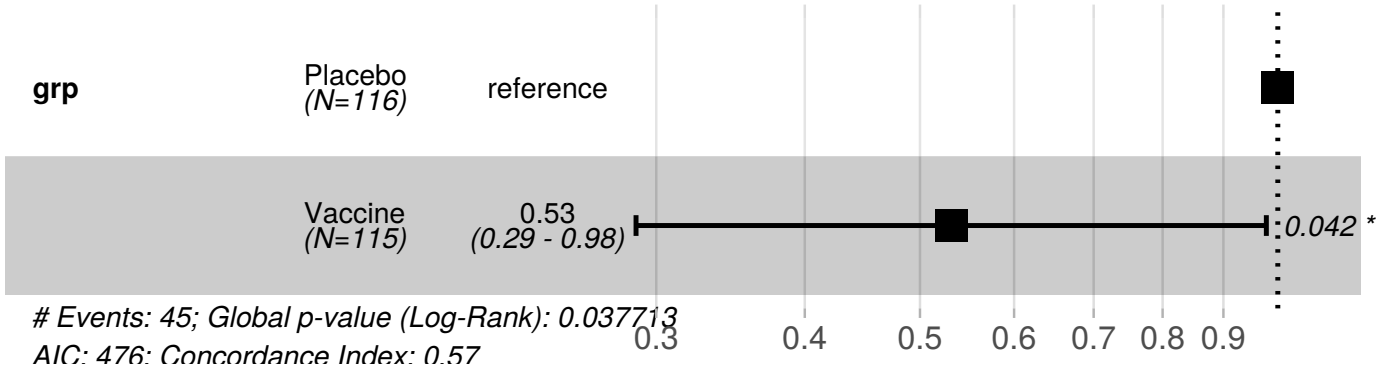

Strata
Placebo
Vaccine
0.3
0.2
0.1
0.0
Cumulative hazard
0
10
20
30
40
50
60
Time

- The hazard ratio (HR) is an expression of the hazard or chance of events occurring in the treatment arm as a ratio of the hazard of the events occurring in the control arm.

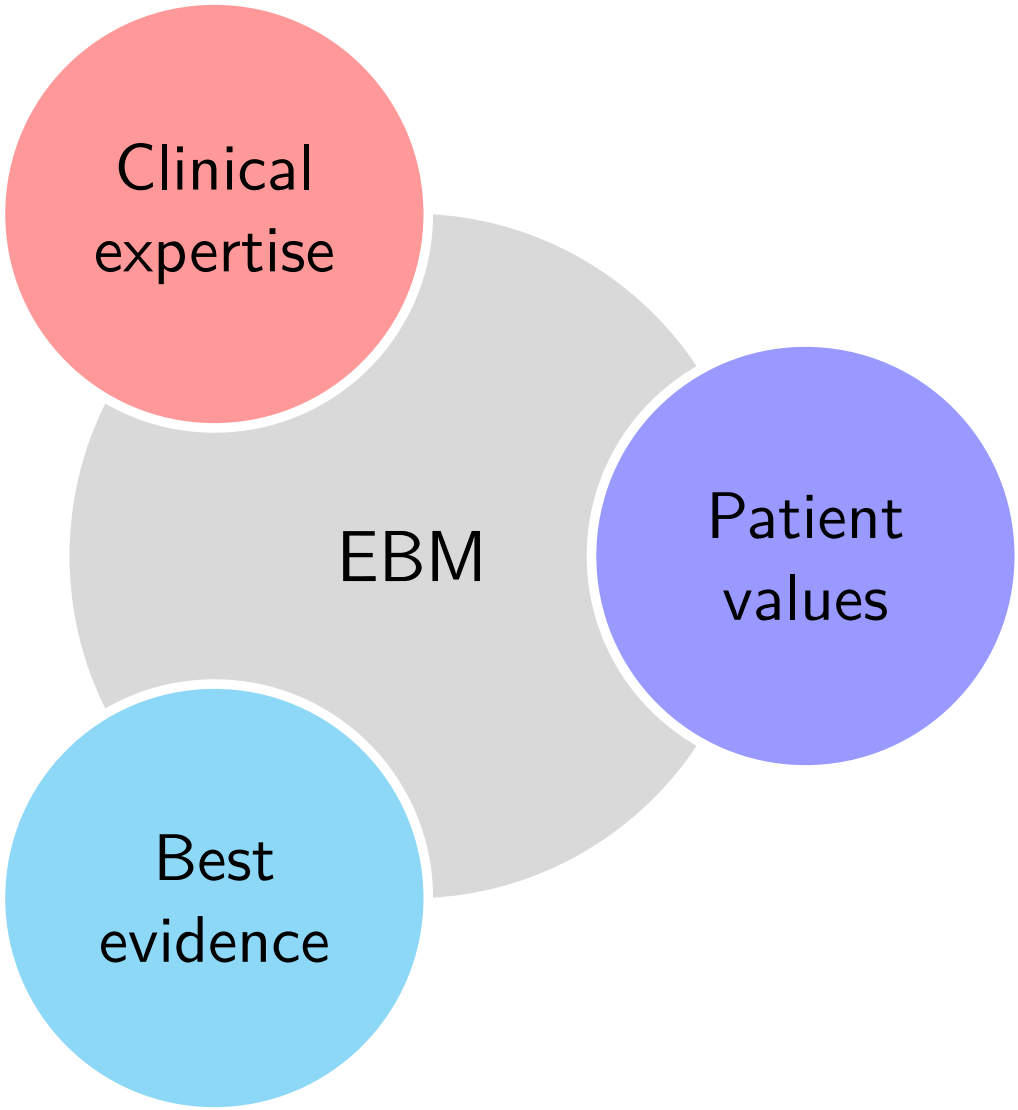
$$HR = \frac{h_{treat}(t)}{h_{control}(t)}$$

- hazard ratio of 2 means that a treated patient who has not yet event by a certain time has twice the chance of having event at the next point in time compared with someone in the control group

HR=1 the factor has no effect
HR>1 the factor is positively associated to the event
HR<1 the factor is negatively associated to the event

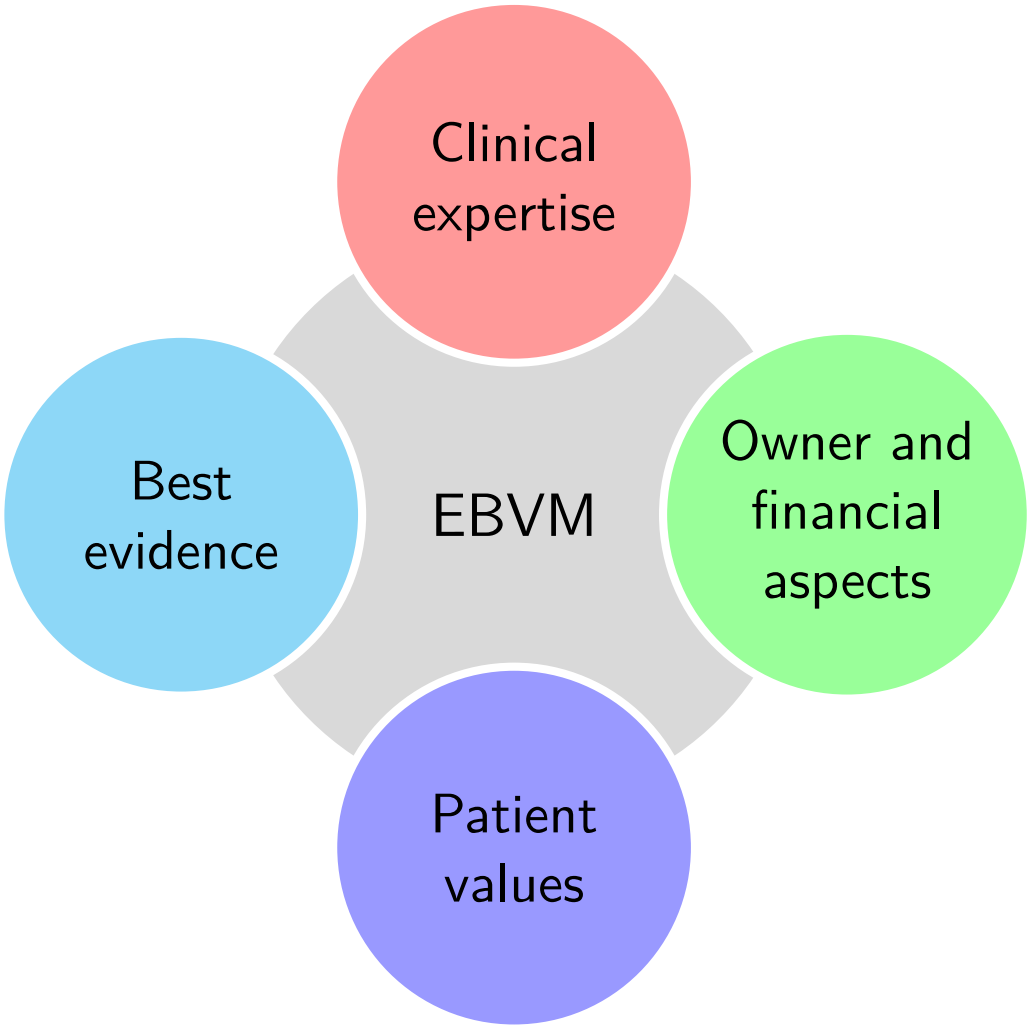


Evidence Based Medicine



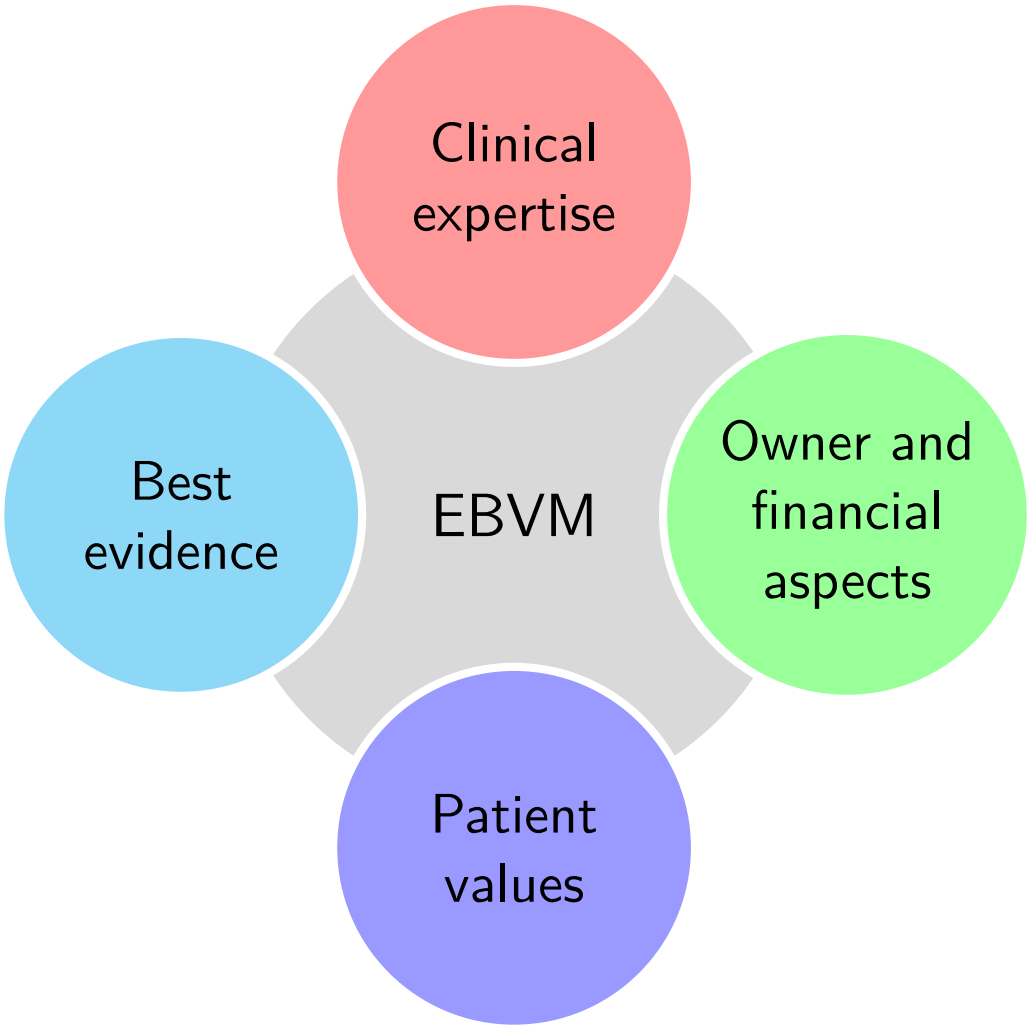
*"Evidence based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual **patients**. The practice of EBM means integrating individual **clinical expertise** with the **best available external clinical evidence** from systematic research."*
(Sackett et al., 2000)

*http://www.ebvmlearning.org/



The practise of Evidence-Based Veterinary Medicine (EBVM) is the use of best available scientific evidence, in conjunction with clinical expertise and consideration of owner and patient factors, to make the best clinical decisions for patients.

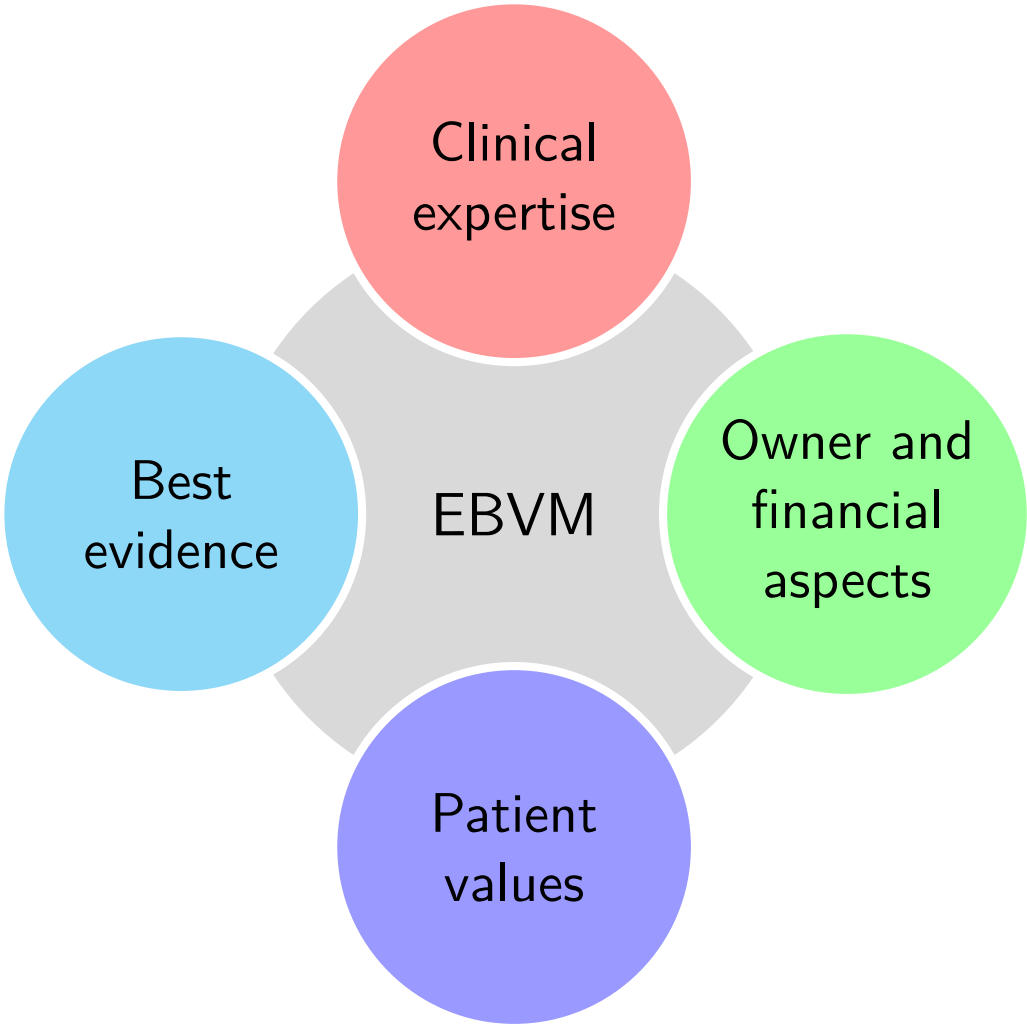
*http://www.ebvmlearning.org/



*"... the primary difference between evidence-based medicine and evidence-based veterinary medicine is that, in the latter, the emphasis must be necessarily placed on **poorer sources of evidence**."* (Kastelic, 2006)

*Over recent decades, there have been massive increases in the availability of **information**, both in the medical and veterinary literature, but also in mainstream media.*

*http://www.ebvmlearning.org/

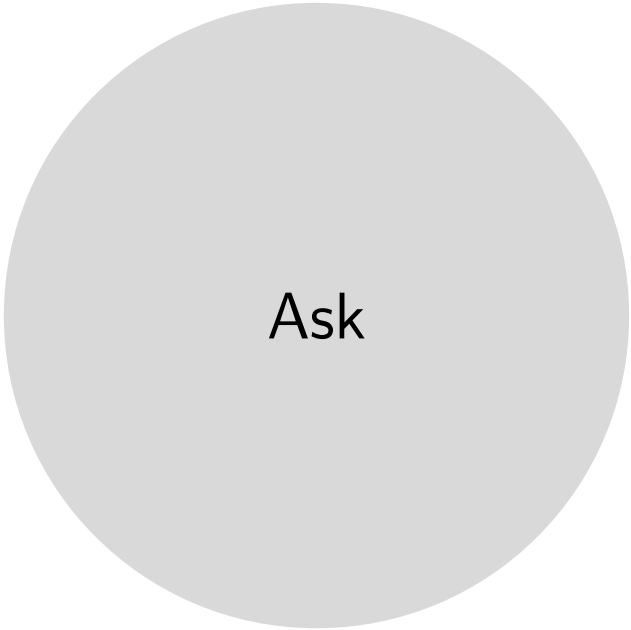


*"**Clients** have access to many of the same resources that veterinary professionals do, but some will lack the clinical knowledge and judgement to assess whether the advice they find online is sensible.*

They may have attempted diagnosis, and even worse, treatment, before seeking veterinary advice, and the veterinary surgeon now has an important role in educating owners and debunking myths."

*http://www.ebvmlearning.org/

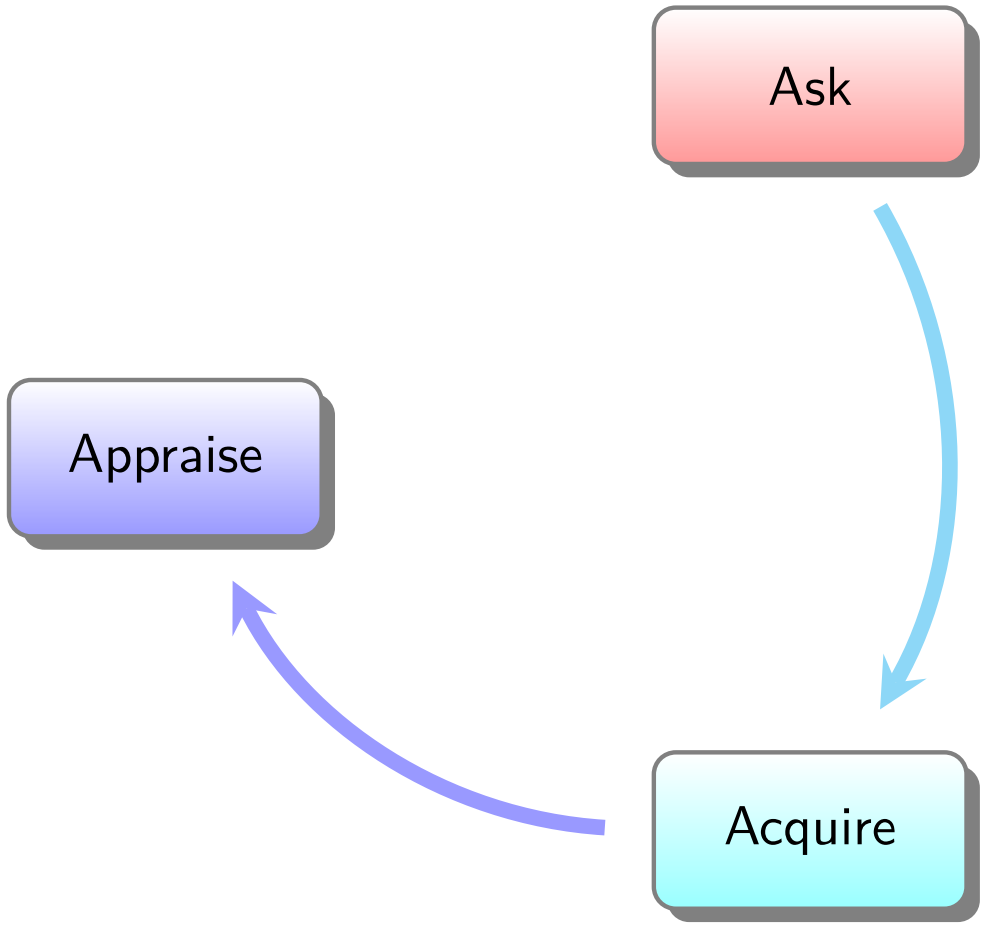
Veterinarians need to be aware of the evidence available, read it, decide on its quality and relevance, and then, if appropriate, incorporate it into clinical decision-making.



defining a clinical question that is of interest and (hopefully!) answerable

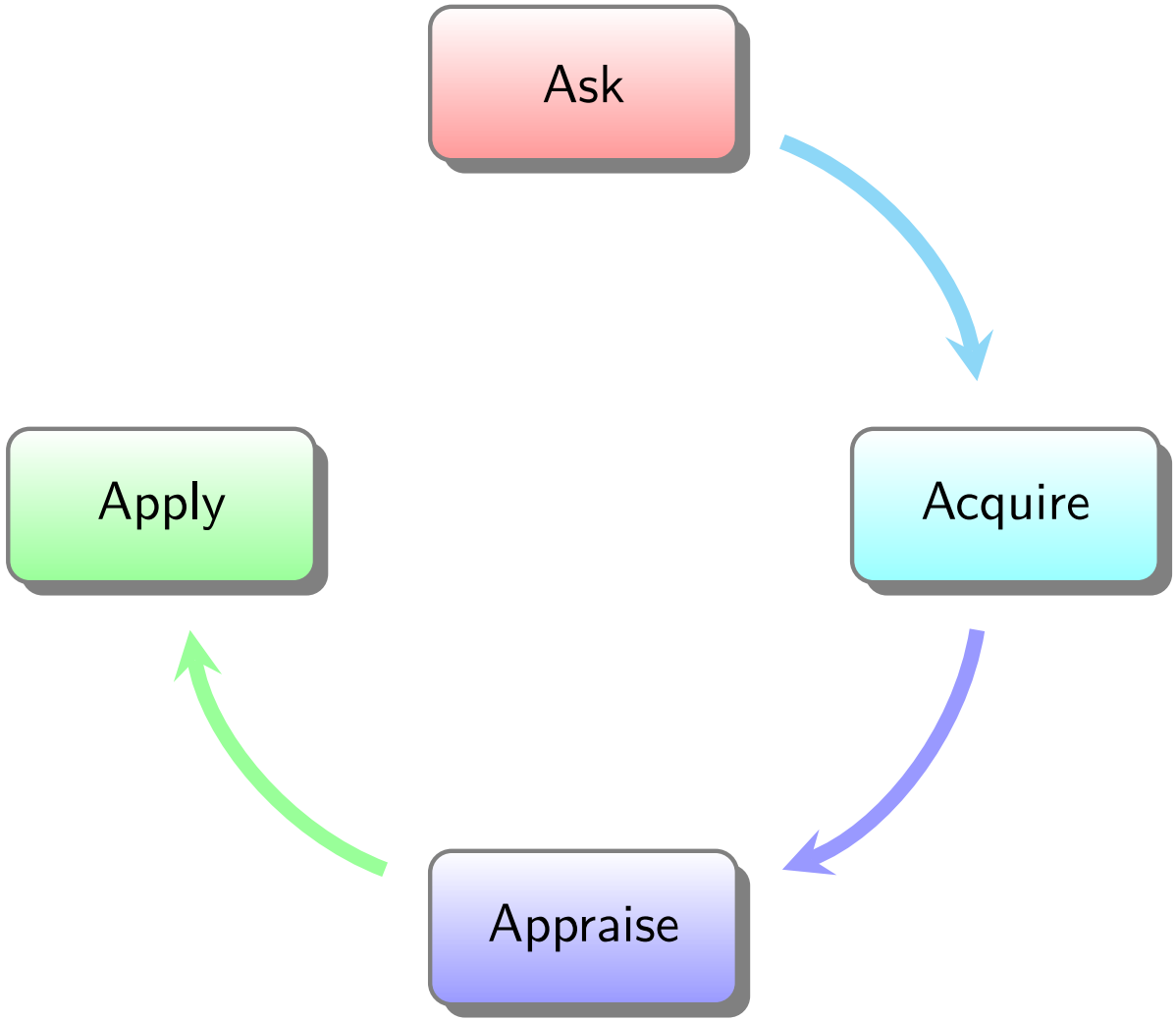
finding the best available evidence to answer the question

*http://www.ebvmlearning.org/



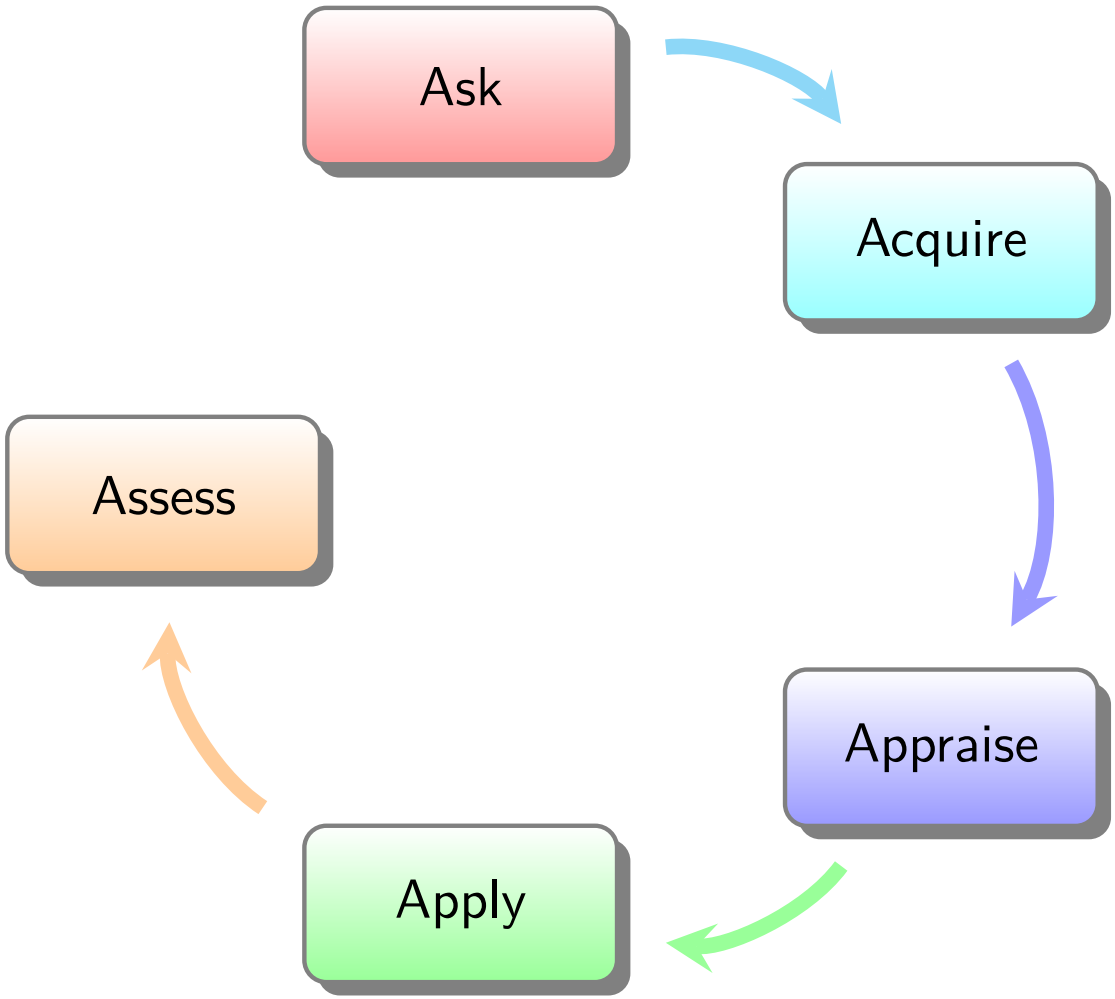
assessing the quality of the relevant evidence found

*http://www.ebvmlearning.org/



implementing the evidence into clinical practice where appropriate

*http://www.ebvmlearning.org/



evaluating the impact of the implementation and changes in clinical practice

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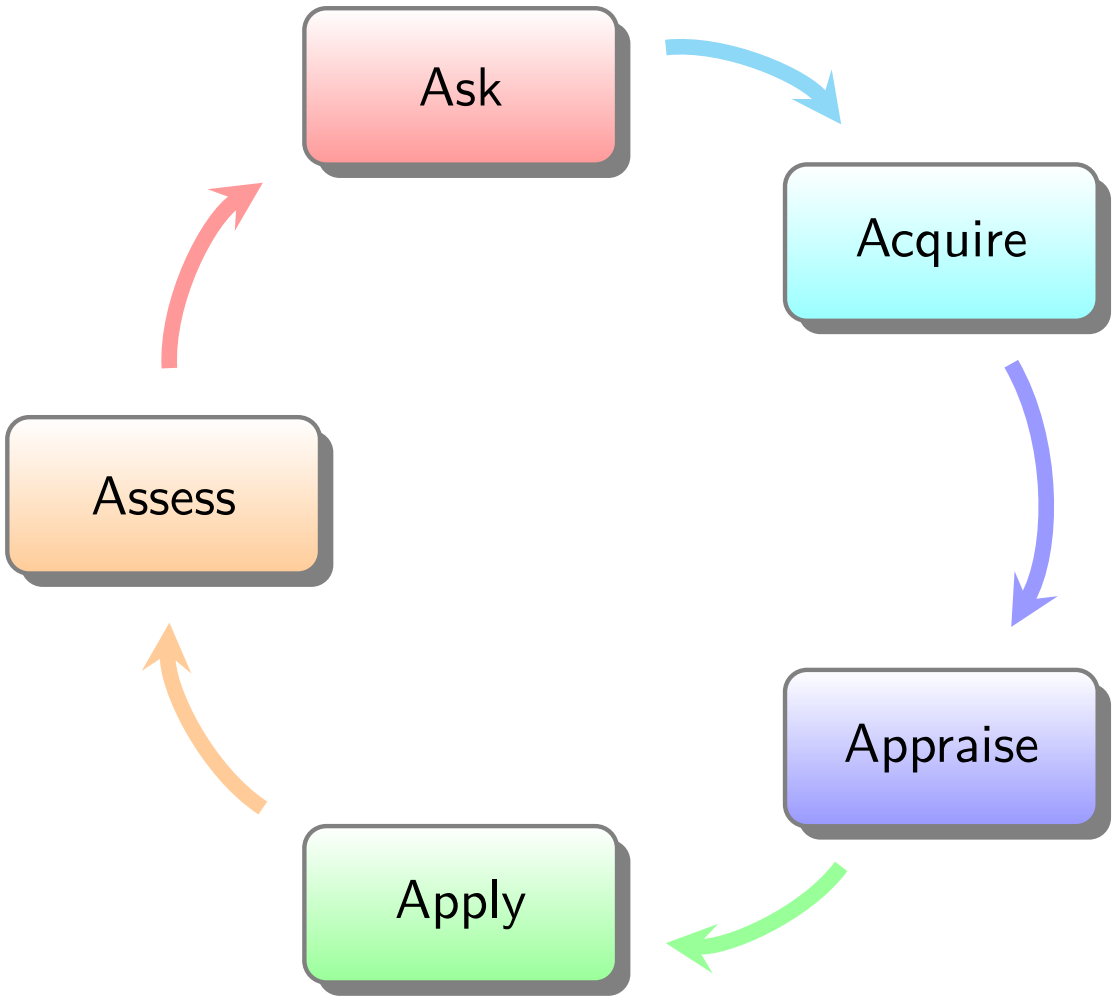
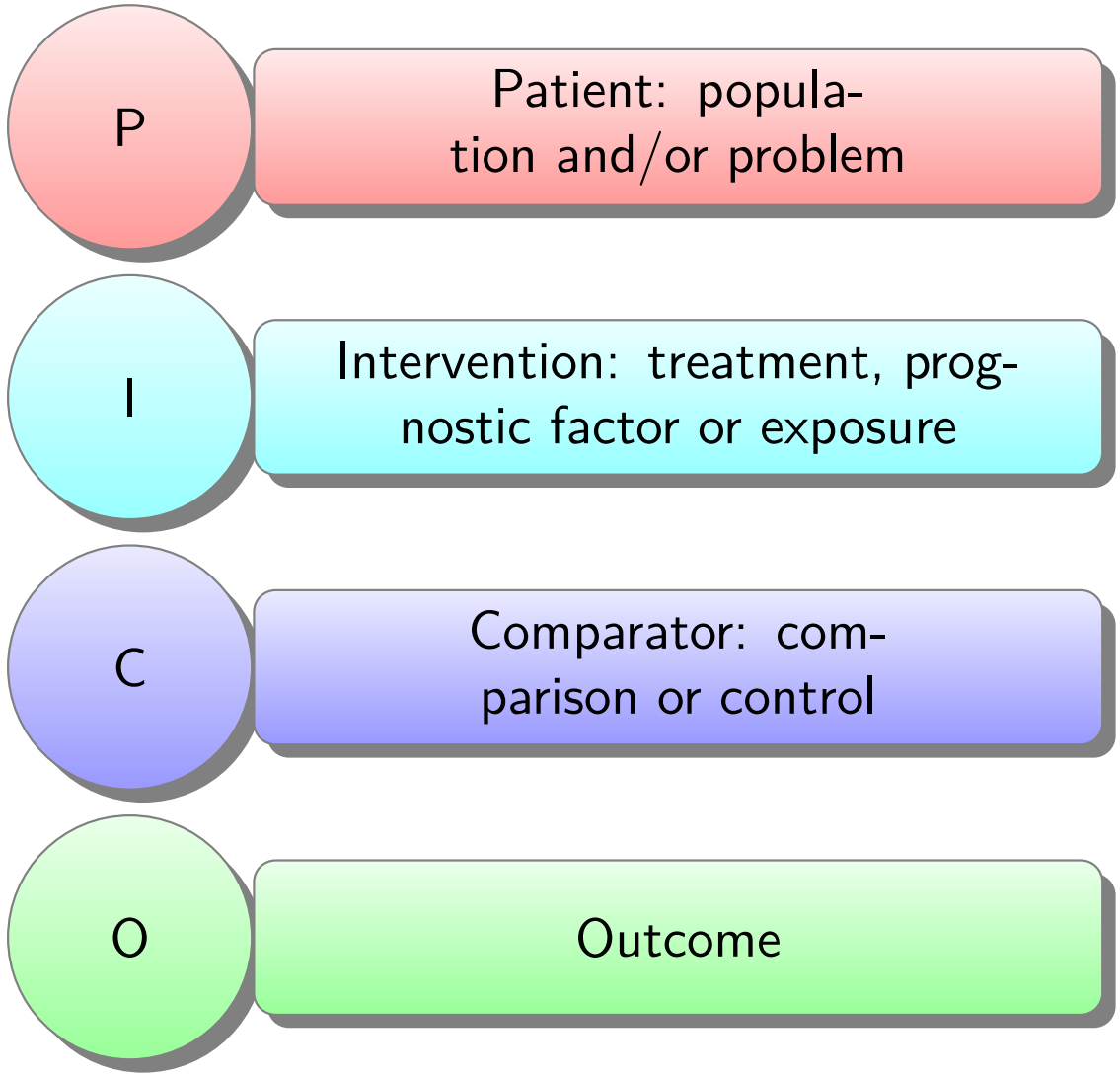


*http://www.ebvmlearning.org/

Formatting your question correctly is important in ensuring that your search for evidence is structured, systematic and complete.

The most common way to format a question is to use the PICO system (`https://pico.vet/`).



*`http://www.ebvmlearning.org/`

Clinical questions can be divided into five main topic areas

Treatment These types of questions refer to treatment choices a veterinarian would need to make in order to achieve a desirable outcome. These choices can include drugs or medicines to be used, surgical methods, changes in diet or management, and many more. These types of questions are best answered by **randomised controlled trials** when they are available.

Which diet is best to feed cats with chronic renal disease?

PICO: In [cats with chronic renal disease] does [feeding a renal prescription diet] compared with [not feeding a renal prescription diet] impact on [survival time]?

*http://www.ebvmlearning.org/

Clinical questions can be divided into five main topic areas:

Prognosis and Incidence These types of questions relate to the likelihood of disease or the progression of disease over time. These questions are best answered by **cohort** studies.

Does sex affect survival in flat-coat retrievers with cancer?

PICO: In [flat-coated retrievers with cutaneous lymphoma], does [being a male] compared with [being a female] affect [average life expectancy]?

*http://www.ebvmlearning.org/

Clinical questions can be divided into five main topic areas:

Aetiology and Risk These types of questions investigate the origin of disease or the factors influencing development of a certain condition or disease. These questions are best answered by **cohort** studies, **case-control** studies or **cross-sectional** studies.

What are the risks of general anaesthesia in ferrets?

PICO: In [ferrets], is [general anaesthesia by triple injectable agent] compared with [general anaesthesia by induction and inhalational agent] associated with [an increased risk of death]?

*http://www.ebvmlearning.org/

Clinical questions can be divided into five main topic areas:

Diagnosis These types of questions involve identification of a disorder based on the animal's presenting signs. These questions are best answered by diagnostic test validation studies (also known as **diagnostic evaluation** studies).

Which diagnostic test is most reliable for diagnosing fascioliasis in dairy cattle?

PICO: In [lactating dairy cattle] does [milk ELISA] compared with [serum ELISA] have [a better sensitivity and specificity for diagnosing fascioliasis]?

*http://www.ebvmlearning.org/

Clinical questions can be divided into five main topic areas:

Prevalence These questions consider the frequency of disease at a certain point in time, and are best answered by **cross-sectional** studies and surveys.

What is the prevalence of cardiac disorders in Welsh Section A mountain ponies?

PICO: In [horses], does [being a Welsh Section A mountain pony] compared with [being any other breed] increase the [prevalence of cardiac disorders]?

*http://www.ebvmlearning.org/

Where to find the evidence?

Ideally, clinical decisions will incorporate the most current and relevant scientific research, but where is the best place to search for the evidence base for veterinary medicine?

Unfortunately, there is no "one-stop-shop", and so a variety of search tools, databases and methods must be used.

- Look for synthesised evidence
- Search the bibliographic databases
- Review the references of relevant papers
- Read key publications
- Contact researchers and experts
- Use unpublished data

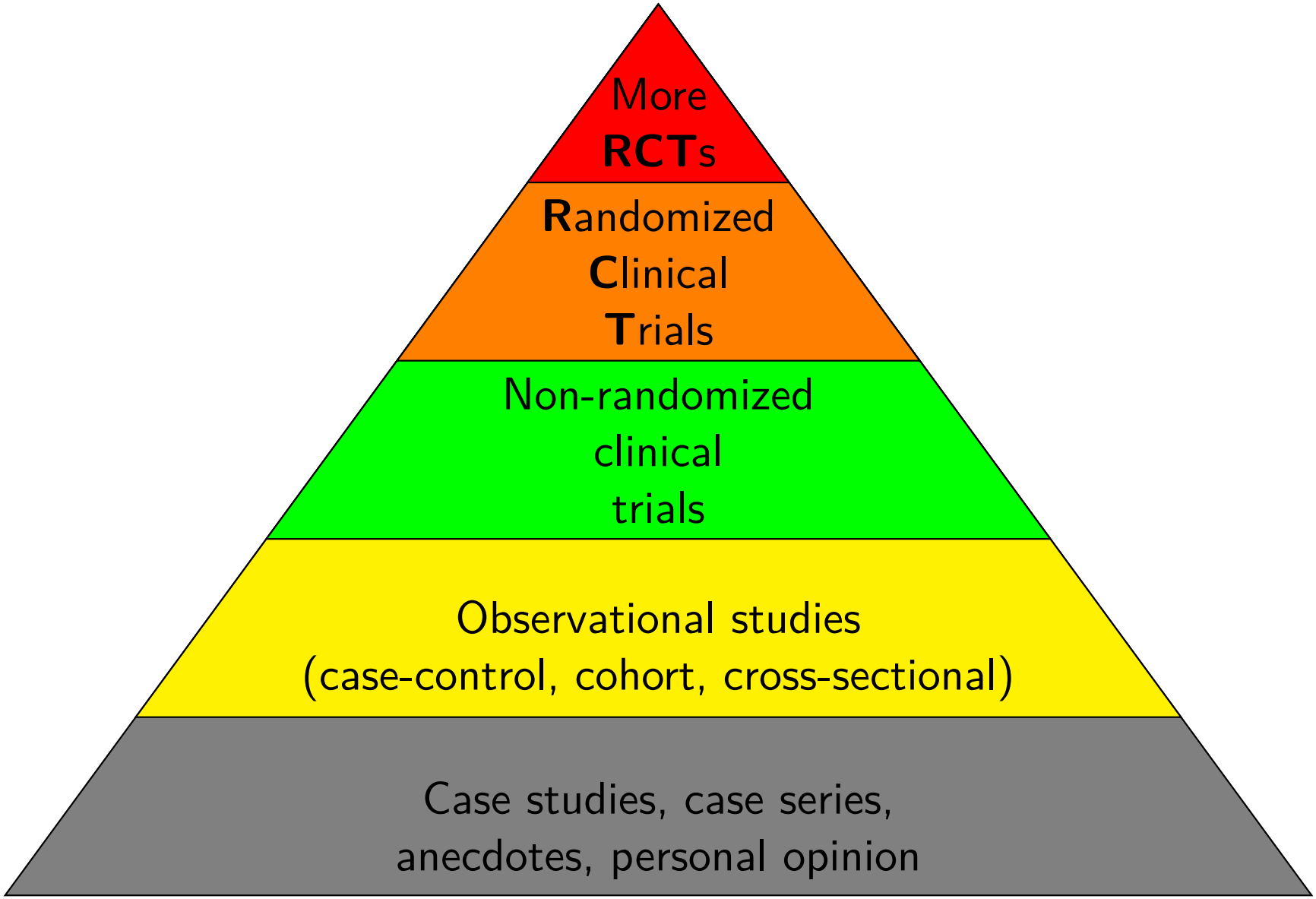
Reporting a search: PRISMA
`http://prisma-statement.org/PRISMAStatement/`

*`http://www.ebvmlearning.org/`

- Does the paper have the right study design to answer my clinical question?
- Is the quality of the paper good enough to help me answer my particular question?
- Is the paper relevant to my clinical question, my population or my patient?
- *Not everything you read is true!*
- *Scientific literature is extremely important, but not always entirely valid.*
- **Which level of evidence does the paper provide?**

*http://www.ebvmlearning.org/

Evidence hierarchy



Hierarchy level: Anecdote

- Acute diarrhea is a common, often self-limiting, cause of presentation for veterinary care, yet there is a paucity of data on frequently-prescribed treatments.
- Two **anecdotally-recommended** treatments: a **probiotic** and **metronidazole**
- Sixty dogs without concurrent comorbidities were randomized into three treatment groups (placebo, probiotic, metronidazole).
- Dogs presenting with acute diarrhea were treated.
- Acceptable fecal consistency after 3.5 ± 2.2 days when receiving probiotic, 4.6 ± 2.4 days with oral metronidazole, and 4.8 ± 2.9 days with placebo.
- $p = 0.17$

*Shmalberg et al. (2019)

Hierarchy level: Non-random allocation trials

- **Bias** is a major problem with non-randomised trials.
- True randomisation involves the use of a formal randomising method and should not be confused with the **arbitrary assignment** of animals to treatments.
- Selecting alternate cases for treatments, or using a **different treatment on certain days of the week** are examples of arbitrary selection and may introduce confounding factors, however unlikely it may seem.
- True randomisation is extremely easy to achieve and is only avoided as a result of ignorance or **laziness**.

*http://www.ebvmlearning.org/

SIGN classification for grading evidence

1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies; for example, case reports, case series
4	Expert opinion

*SIGN: Scottish Intercollegiate Guidelines Network

Applying evidence to practice

- How relevant is the evidence?
- Discuss important evidence
- Prepare a strategy for change:
  - Who?
  - When?
  - What?
  - How?
- If you're still not convinced that the evidence fully pertains to you, one way to start putting evidence into practice might be to run a sort of **'pilot'** to assess the possible effects of your new approach in the context of your practice.

*http://www.ebvmlearning.org/

The only way we can establish if the care of patients is improved by the application of evidence to practice is to measure the effect of the apply stage.

It is vital to assess what we do in practice in order to ensure our practice is moving with the times and adapting and responding to the advances in the profession.

A simple way of assessing your own performance as an EBVM practitioner is to **ask yourself some questions**, and to provide truthful answers!

Some suggested questions are:

- Do I identify and prioritise problems to be solved (specifically in relation to what information I need to make my best decisions)?
- Do I perform a competent and complete examination of each animal, in order to establish the likelihood of alternative diagnoses?

*http://www.ebvmlearning.org/

- Do I have an accurate knowledge of disease manifestations, the sensitivities and specificities of the clinical signs I am looking for, and the frequency of occurrence of different combinations of clinical signs within a disease?
- Do I search for missing information when I know I am lacking it?
- Do I appraise information I am given in terms of scientific validity?
- Do I understand terms such as specificity and sensitivity, which enable me to interpret important information in my daily practice?
- Do I have the resources to access the Internet and use these to the best of my ability?
- Am I aware of the veterinary information databases?
- Do I actively consider if the application of new information I am given is scientifically justified and sensible for the situation to which I might apply it?
- Do I explain the pros and cons of the different options to owners, taking into account and making clear their different utilities?

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Narrative reviews:

- Tend to cover a subset of studies based on availability or author selection.
- This can introduce an element of selection bias.

Systematic reviews:

- Employ standardised and rigorous methodologies to review scientific literature, with a view to minimising bias.
- They conduct a comprehensive literature search to identify, appraise, and synthesise all the relevant studies on a particular topic.
- They will formally and openly report the sources they use as well as the search strategies used to find those sources, so that searches can be peer-reviewed and replicated.
- Evidence synthesis:

  meta-synthesis: if a systematic review inspects qualitative data
  meta-analysis: if homogenous quantitative evidence is assessed

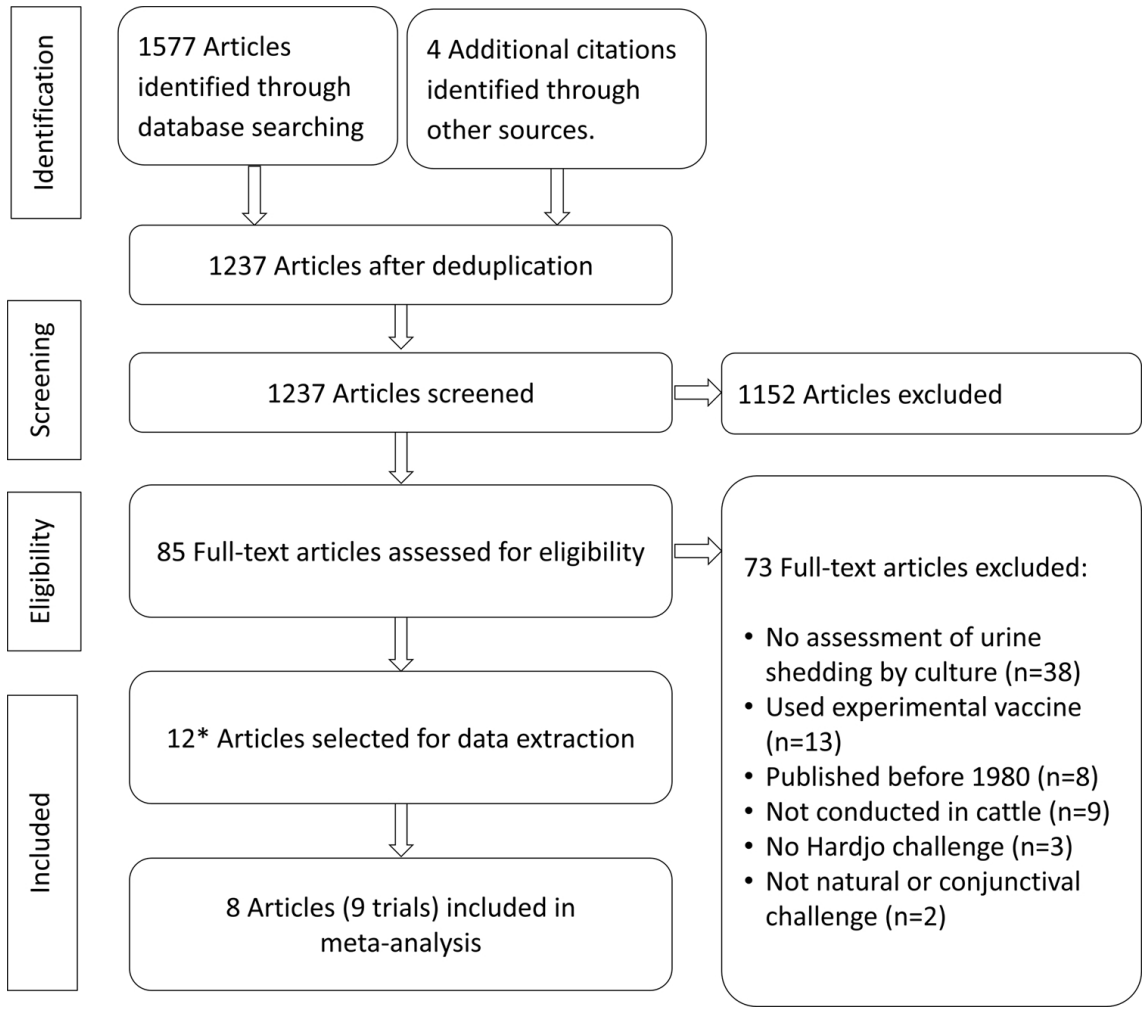
*http://www.ebvmlearning.org/

"A collection of techniques whereby the results of two or more independent studies are statistically combined to yield an overall answer to a question of interest."

- Fixed effects (**FE**) model:
  - assumes that each observed individual study result is estimating a common unknown overall pooled effect
  - the research question concerns whether treatment has produced an effect, on the average, in the set of **studies being analysed**
  - there is **no interest in generalising** the results to other studies.

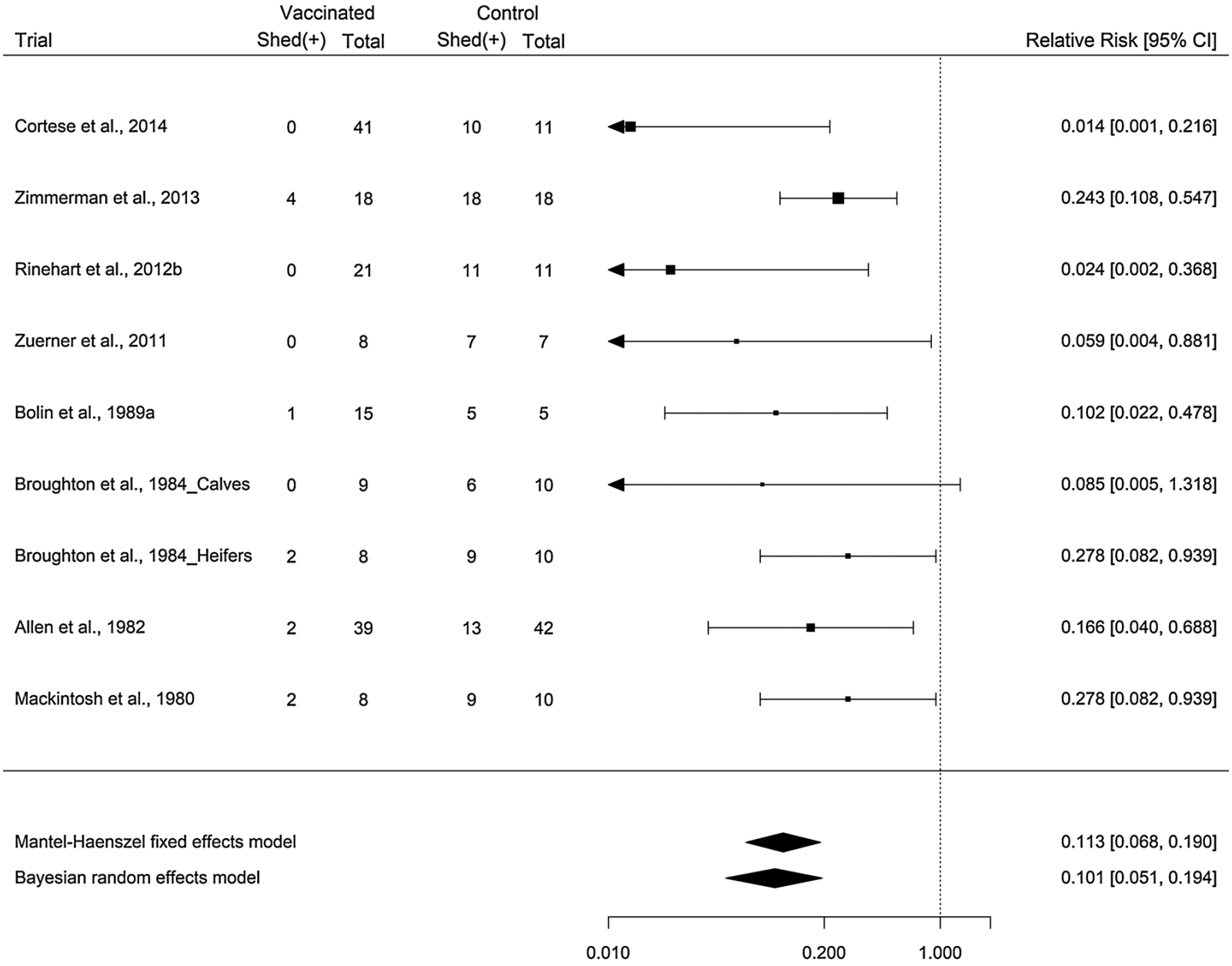
- Random effects (**RE**) model:
  - assumes that each individual observed result is estimating its own unknown underlying effect
  - is estimating a common population mean
  - allows for the existence of **between-study** heterogeneity as well as within-study variability
  - when the research question involves extrapolation to the **future**

- Leptospirosis is a **zoonosis** often associated with occupational exposure from livestock that can be prevented by animal vaccination.
- Several trials have assessed vaccine efficacy in livestock but there have been **no attempts** to evaluate these trials **jointly**.
- This systematic review and meta-analysis aimed to estimate vaccine **efficacy to prevent urinary shedding** of *Leptospira serovar Hardjo (Hardjo)* in cattle.



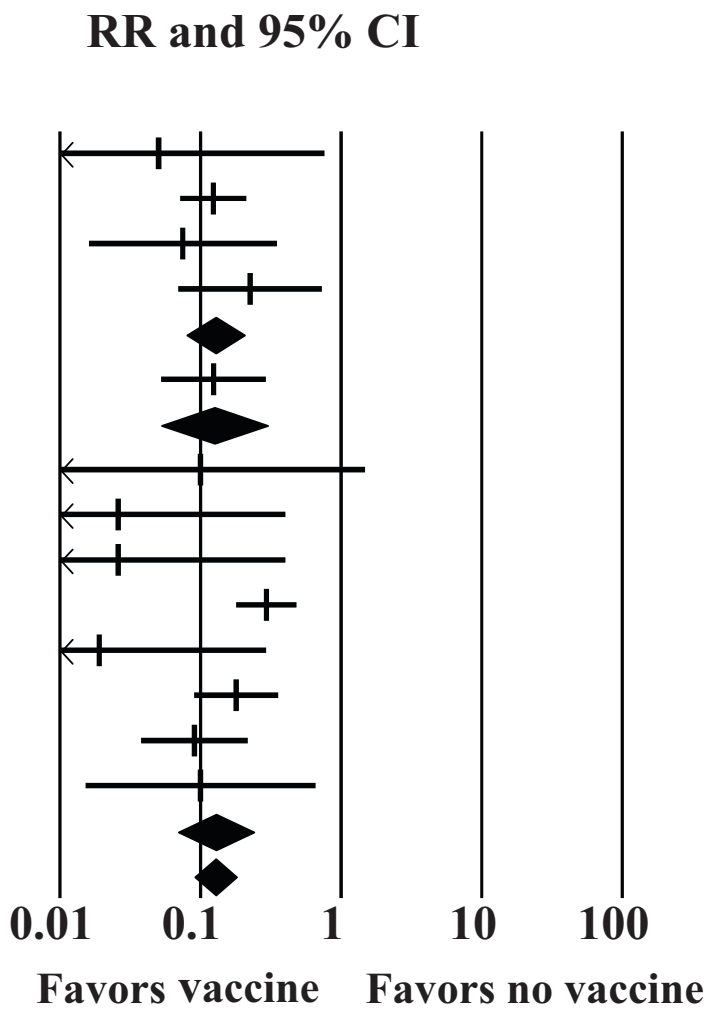
PRISMA Flow Diagram

*Sanhueza et al. (2018)



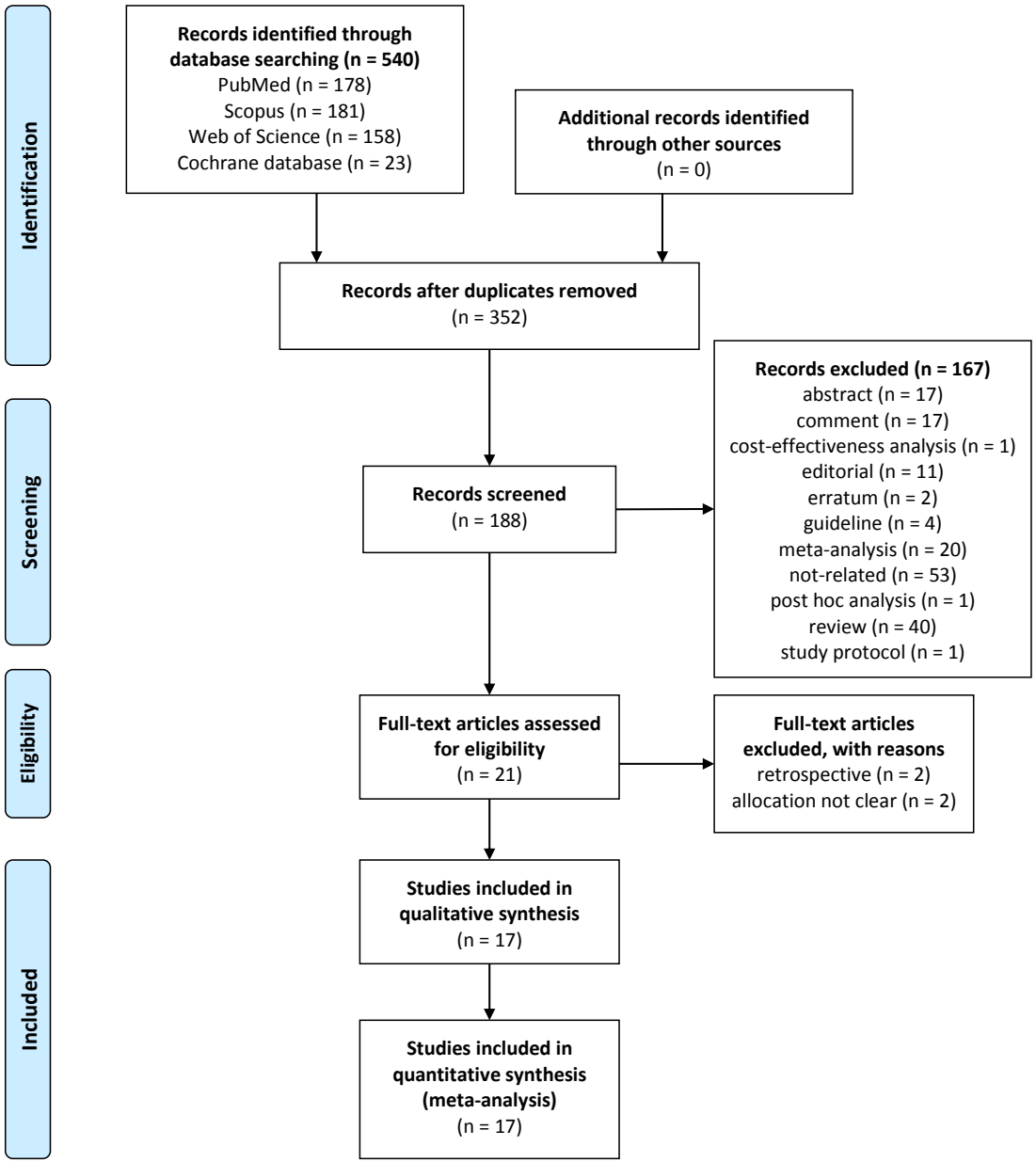
*Sanhueza et al. (2018)

Virus serotype	Study	RR	Lower limit	Upper limit
A	Brehm, 2008	0.051	0.003	0.770
A	Goris, 2008	0.123	0.071	0.214
A	Graves, 1968	0.075	0.016	0.352
A	Mattion, 2004	0.225	0.069	0.737
PRR A		**0.126**	**0.079**	**0.202**
Asia 1	Salt, 1995	0.124	0.052	0.295
PRR Asia 1		**0.124**	**0.052**	**0.295**
O	Aggarwal, 2002	0.100	0.007	1.490
O	Cox, 2005	0.026	0.002	0.406
O	Cox, 2006	0.026	0.002	0.406
O	Cox, 2007	0.294	0.177	0.488
O	Doel, 1994	0.019	0.001	0.297
O	Donaldson, 1989	0.179	0.089	0.361
O	Goris, 2007	0.090	0.037	0.219
O	Orsel, 2005	0.100	0.015	0.664
PRR O		**0.127**	**0.068**	**0.236**
Overall PRR		**0.126**	**0.089**	**0.178**



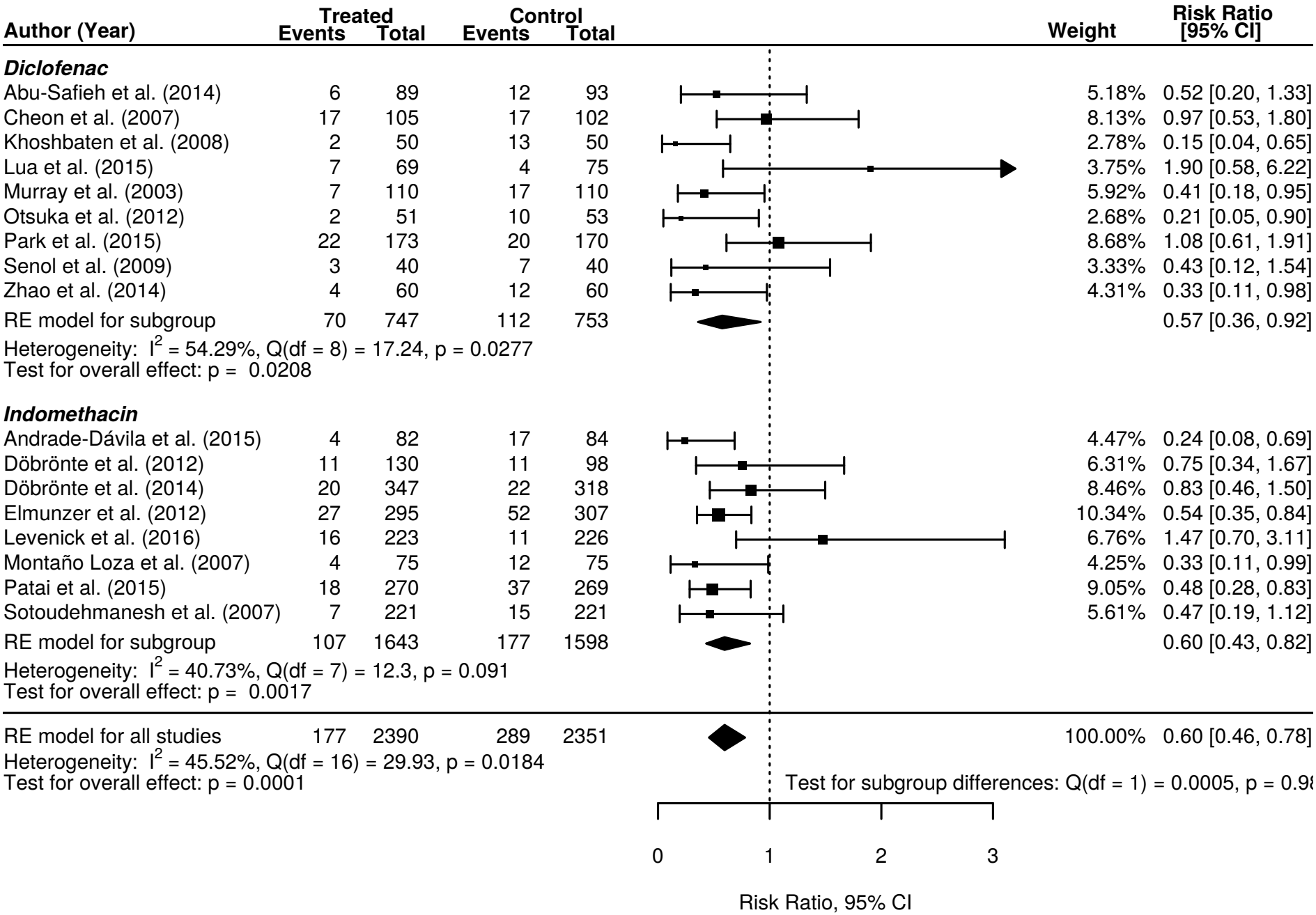
FMD: Forest plot of the relative risk (RR) of the clinical disease in vaccinated cattle for each of the 13 included studies, the pooled RR (PRR) per virus serotype and the overall PRR together with the 95% CI.

*Halasa et al. (2011)



*Patai et al. (2017)

- The greatest challenges for **endoscopists** performing biliary therapy in **endoscopic retrograde cholangiopancreatography** (ERCP) are to achieve selective biliary cannulation and prevent **post-ERCP pancreatitis** (PEP).
- Non-steroidal anti-inflammatory drugs have proven **prophylactic** effect in PEP.
- **Diclofenac** and **indomethacin** are the most studied drugs for preventing post-ERCP pancreatitis (PEP).
- Our aim was to evaluate **all prospective trials** published in full text that studied the efficacy of diclofenac or indomethacin and were controlled with placebo or non-treatment for the prevention of PEP in adult patients undergoing ERCP.


Author (Year)
Treated Events Total
Control Events Total
Weight
Risk Ratio [95% CI]
Diclofenac
Abu-Safieh et al. (2014) 6 89 12 93 5.18% 0.52 [0.20, 1.33]
Cheon et al. (2007) 17 105 17 102 8.13% 0.97 [0.53, 1.80]
Khoshbaten et al. (2008) 2 50 13 50 2.78% 0.15 [0.04, 0.65]
Lua et al. (2015) 7 69 4 75 3.75% 1.90 [0.58, 6.22]
Murray et al. (2003) 7 110 17 110 5.92% 0.41 [0.18, 0.95]
Otsuka et al. (2012) 2 51 10 53 2.68% 0.21 [0.05, 0.90]
Park et al. (2015) 22 173 20 170 8.68% 1.08 [0.61, 1.91]
Senol et al. (2009) 3 40 7 40 3.33% 0.43 [0.12, 1.54]
Zhao et al. (2014) 4 60 12 60 4.31% 0.33 [0.11, 0.98]
RE model for subgroup 70 747 112 753 0.57 [0.36, 0.92]
Heterogeneity: I^2 = 54.29%, Q(df = 8) = 17.24, p = 0.0277
Test for overall effect: p = 0.0208
Indomethacin
Andrade-Dávila et al. (2015) 4 82 17 84 4.47% 0.24 [0.08, 0.69]
Döbrönte et al. (2012) 11 130 11 98 6.31% 0.75 [0.34, 1.67]
Döbrönte et al. (2014) 20 347 22 318 8.46% 0.83 [0.46, 1.50]
Elmunzer et al. (2012) 27 295 52 307 10.34% 0.54 [0.35, 0.84]
Levenick et al. (2016) 16 223 11 226 6.76% 1.47 [0.70, 3.11]
Montaño Loza et al. (2007) 4 75 12 75 4.25% 0.33 [0.11, 0.99]
Patai et al. (2015) 18 270 37 269 9.05% 0.48 [0.28, 0.83]
Sotoudehmanesh et al. (2007) 7 221 15 221 5.61% 0.47 [0.19, 1.12]
RE model for subgroup 107 1643 177 1598 0.60 [0.43, 0.82]
Heterogeneity: I^2 = 40.73%, Q(df = 7) = 12.3, p = 0.091
Test for overall effect: p = 0.0017
RE model for all studies 177 2390 289 2351 100.00% 0.60 [0.46, 0.78]
Heterogeneity: I^2 = 45.52%, Q(df = 16) = 29.93, p = 0.0184
Test for overall effect: p = 0.0001
Test for subgroup differences: Q(df = 1) = 0.0005, p = 0.9
0
1
2
3
Risk Ratio, 95% CI

- Cochrane Library
- Joanna Briggs Institute
- Campbell Collaboration
- Centre for Evidence-Based Medicine
- NHS Centre for Reviews and Dissemination
- Bandolier
- PubMed Clinical Queries: Find Systematic Reviews

- RCVS Knowledge
- The Centre for Evidence-based Veterinary Medicine at the University of Nottingham
- Veterinary Evidence

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