Exploring the use of Bayesian statistical models to reduce the number of animals in control groups

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Inspired by patients.
Driven by science.

Outline

Motivation

- Using historical data via a Bayesian analysis to reduce animal numbers

Case study

First steps

Types of control groups

Bayesian methodology

Summary to date

Motivation

Using historic data
– it's a part of life!

"Forewarned is forearmed"

"The best qualification of a prophet is to have a good memory. "

--Marquis of Halifax

…. Used in assessing hazards

http://www1.secam.ex.ac.uk/famous-forecasting-quotes.dhtml Marquis of Halifax quote

Motivation

Comparable available historic data

Desire to reduce animal numbers

Need to compare compounds across days/experiments

Case study

Background

Mouse model to study inflammatory response after a challenge.

Measures a number of cytokines at 2.5 or 3hrs.

Includes test compounds + three control treatments:

- Negative group (no challenge).
- ‘Positive’ group (challenge, no treatment).
- Comparator with known efficacy

Main comparisons of interest:

- Test compound vs. +ve group (untreated) – Does test compound reduce the response?

Data on 19 studies available (reasonably consistent protocol).

Most frequent in-vivo assay in this therapeutic area.

Data typically presented an experiment at a time, in PRISM

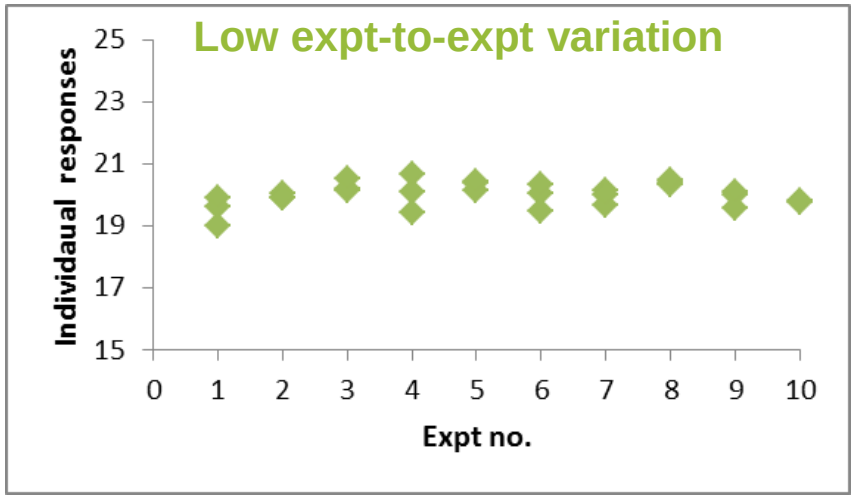
First steps

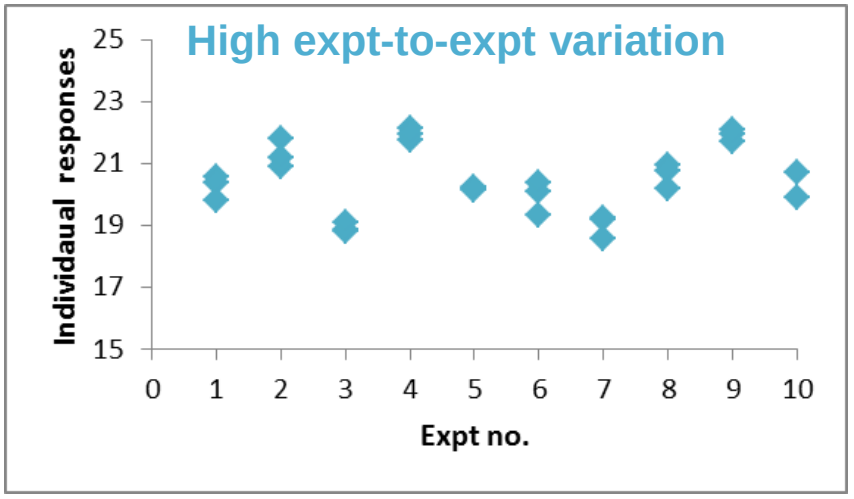
QC charts for control groups

Well received.

Introduces the idea of expt-to-expt variation.

Intuitively, the relevance of the historic controls depends on the size of the study to study variation.





Bayesian analysis can use the historic control information, down-weighting it according to the amount of experiment-to-experiment variation

Types of control groups

- Not used for formal statistical comparisons. Example uses:
  - To ensure challenge is working; to establish a “window”; to check consistency with previous studies; to convert values to %.
  - Replace group with a range from a predictive distribution

- Used for formal comparison vs. test compounds/doses
  - Used as the comparison in t-tests ..etc
  - Combine down-weighted historic data with the current experiment

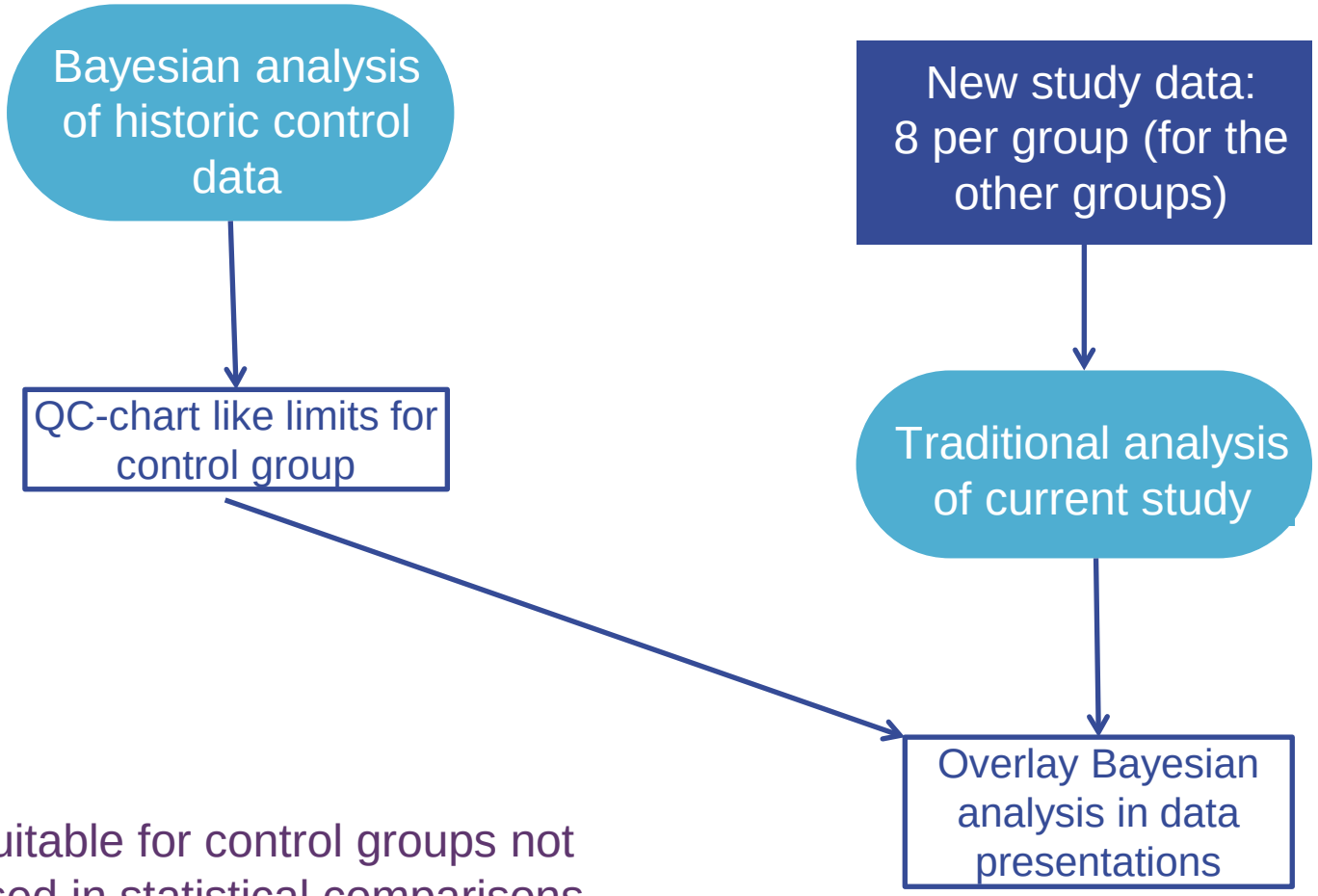
Bayesian methodology

Outline

- Analyse historic control treatment group data, excluding the last study.
  - Bayesian meta-analysis
- Analyse the last study
  - Show what would have happened if we had “bought into” the Bayesian approach; omit animals if necessary
- Possible options for future studies:
  - Omit all/some animals from all/some control groups.
  - Use historic data as prior information combined with observed data in a Bayesian analysis.
  - Use historic data to give a predictive distribution for control group. i.e. don’t include that treatment group in current study.
- Statistical model based on meta-analytic predictive methodology in Neuenschwander et al

Bayesian methodology (2)

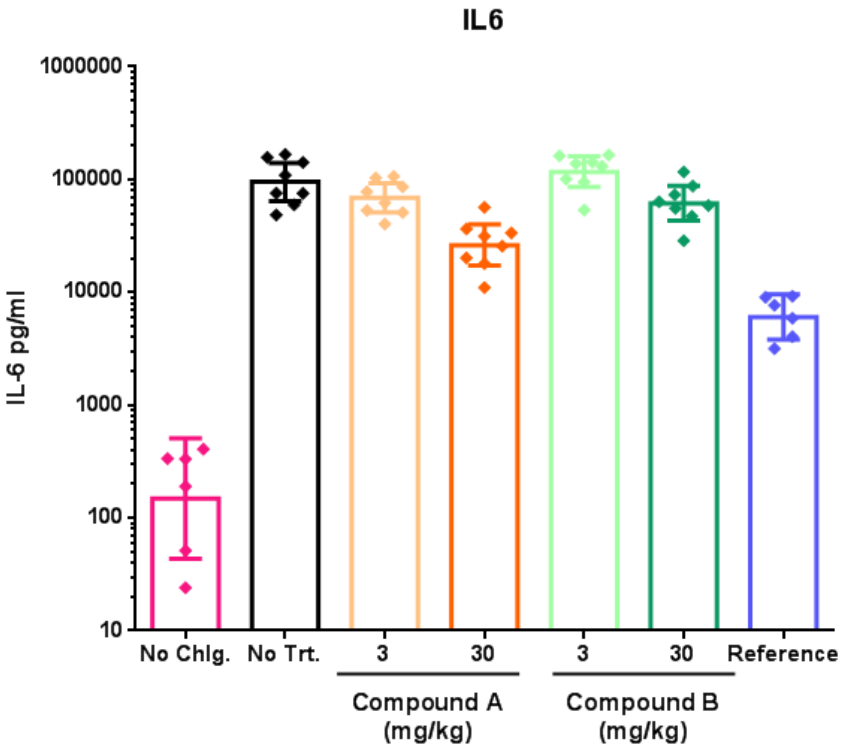
> **"Replacing" control groups with predictive distributions**

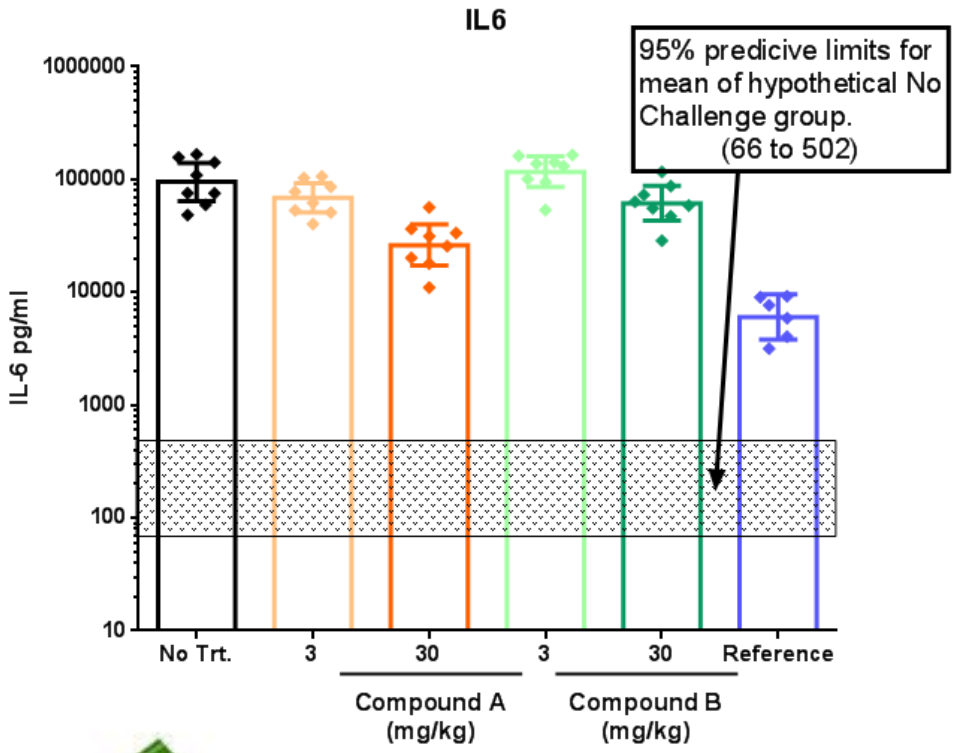


Suitable for control groups not used in statistical comparisons

Case study

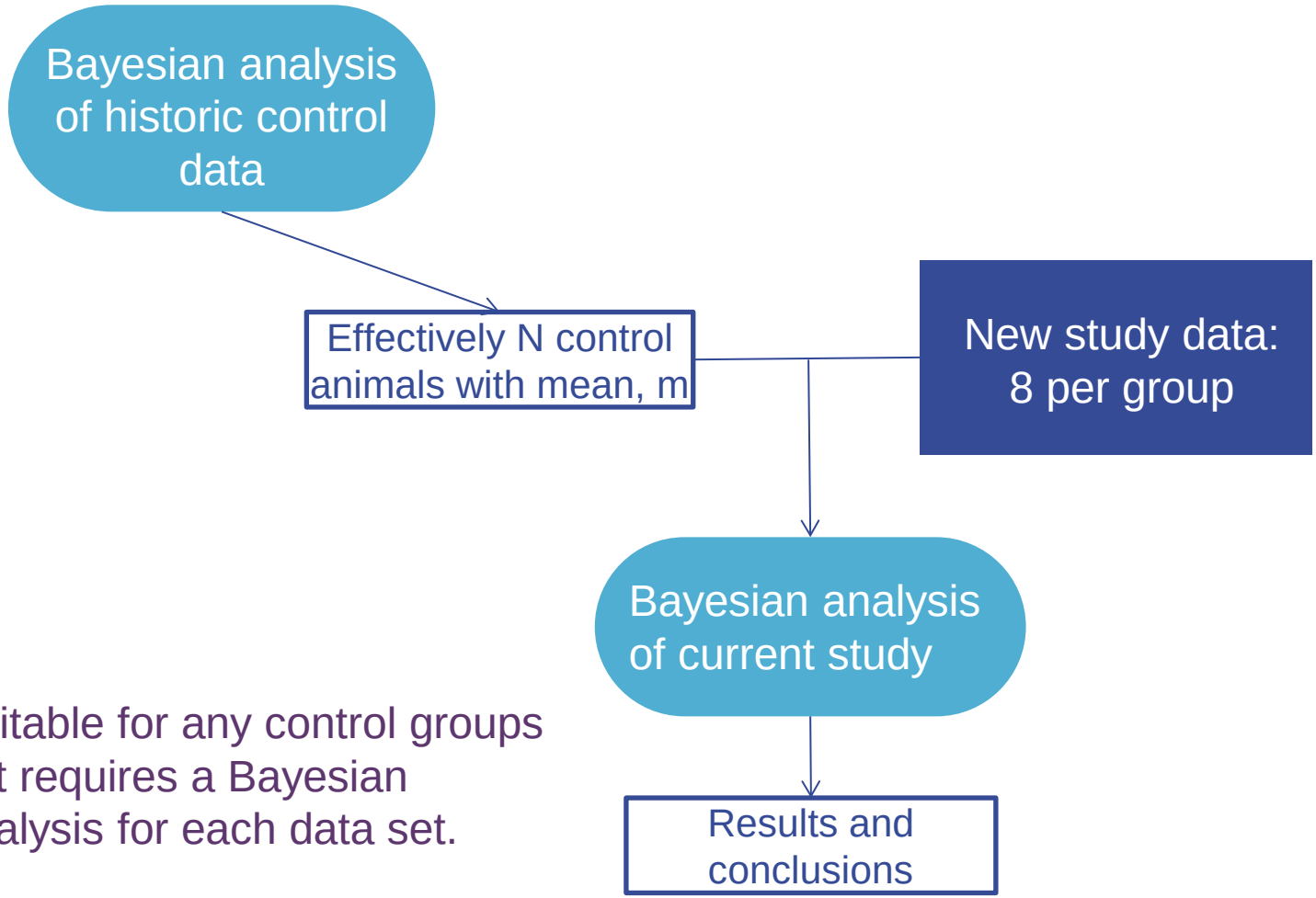
Predictive distribution





Bayesian methodology (4)

Full Bayesian analysis

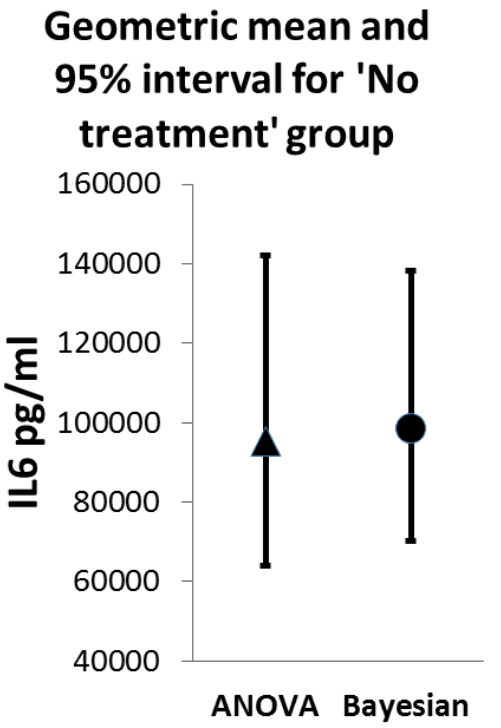


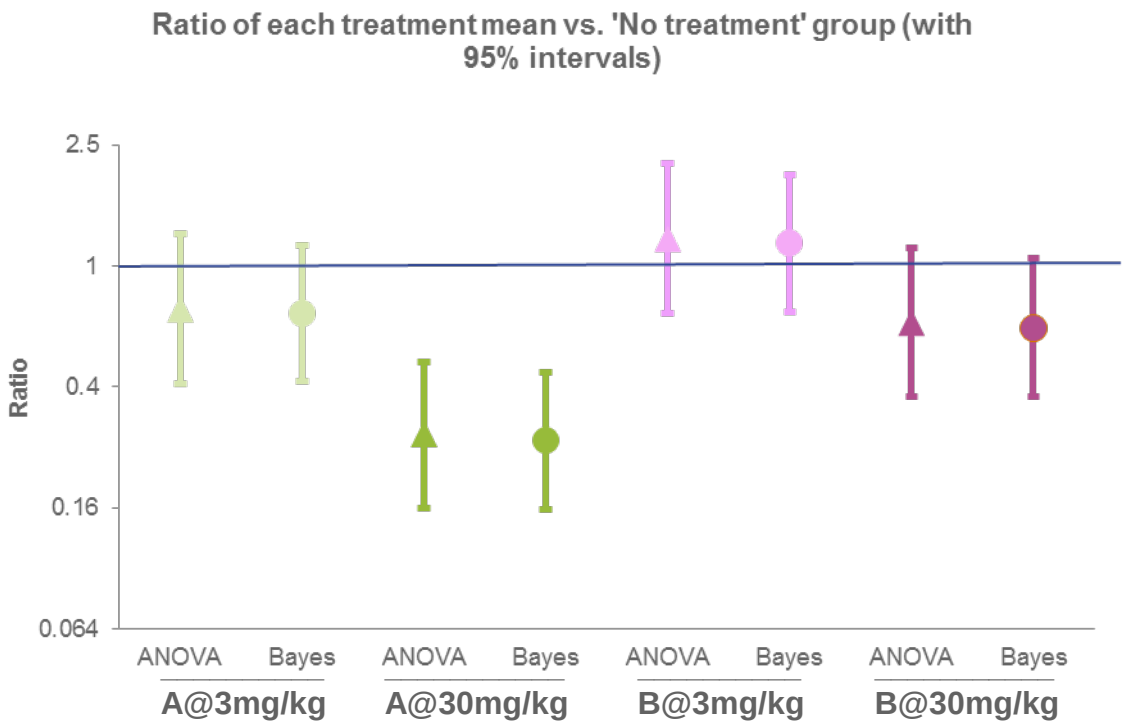
Suitable for any control groups but requires a Bayesian analysis for each data set.

Case Study

Full Bayesian analysis

The Bayesian analysis gives narrower confidence intervals. It is comparable to using 3 extra animals (11 instead of 8)





Summary to date

Bayesian methods can reduce required resource (animal numbers)

To have the greatest impact, focus on studies repeated very frequently

QC charts provided an excellent introduction to between and within study variation

Predictive approach developed for two models

Biologists very positive; implementation underway

Potential saving: one control group per study

Full Bayesian approach developed for two models

Modest savings in numbers of animals in case study presented here

More savings in the other pilot case – but assay is no longer run

Software issue; potentially lengthening turnaround times for rapid screens

Biologists suggested using a slightly less frequent assay as a pilot

Reference

Walley R, Sherington J, Rastrick J, Detrait E, Hanon E and Watt G Using Bayesian analysis in repeated preclinical in vivo studies for a more effective use of animals. Pharmaceutical Statistics 2016; 15(3):277-285, DOI: 10.1002/pst.1748

Questions?

Thanks!

Bayesian meta-analytic predictive approach

Statistical model based on Neuenschwander et al (2010)

- Historic data:, h=1…H:

Observed study data: $Y_h \mid \theta_h, \sigma_a^2 \sim N(\theta_h, \sigma_a^2)$

Study means: $\theta_1 \ldots \theta_H \sim N(\mu, \tau^2)$

- Predictions for next study, denoted by *:

True study mean $\theta^* \sim N(\mu, \tau^2)$ $\Rightarrow$ prior for next study

Observed study mean $\bar{Y}^* \mid \theta^*, \sigma_a^2 \sim N(\theta^*, \sigma_a^2/n^*)$ $\Rightarrow$ predictive dn for next study

- Priors and hyperpriors

μ has vague normal prior

T has vague half normal prior (sensitivity analysis carried out)

σ_a^2 has vague gamma prior