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IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

# Applications of Bayesian methods in health technology assessment

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# Outline



- Introduction
  - Bayesian vs. frequentist methods
  - IQWiG methods paper
- Bayesian methodology in HTA
  - Clinical trials
  - Economic evaluations
  - (Network) meta-analysis
- Meta-analysis with very few studies
- Discussion
- Conclusion
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# Introduction



Definition of Bayesian methods in HTA:

*"The explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation, and reporting of a health technology assessment."*

(Spiegelhalter et al., 1999)

With this very general definition almost all HTA reports are based upon Bayesian methods, because almost always multiple sources are used, e.g., the main meta-analysis of RCTs for the benefit assessment AND registry data for epidemiological questions.

# My understanding

## Frequentist methods:

- Point and interval estimation of relevant parameters
- Significance testing
- Output: Point estimates, confidence intervals, *p*-values

## Bayesian methods:

- Specification of prior distributions
- Calculation of posteriori distributions from prior distribution and likelihood
- Output: Expected values, credible intervals, Bayes factors

# The IQWiG methods paper

- Version 1 (2005):
  Just a note that Bayesian methods exist in the context of model uncertainty.

- Versions 2 (2006) and 3 (2008):
  Bayesian methods mentioned as general alternative to frequentist methods and that IQWiG will apply Bayesian methods "where necessary".

- Versions 4.0 (2011) and 4.1 (2013):
  Designation of indirect comparisons as possible application area for Bayesian methods.

https://www.iqwig.de/de/methoden/methodenpapier.3020.html

# The IQWiG methods paper

- Version 4.2 (2015):
  Use of Bayesian methods mentioned for health economic evaluations and indirect comparisons.
- Version 5.0 (2017):
  Use of Bayesian methods mentioned for health economic evaluations, indirect comparisons, and pairwise meta-analyses with very few studies.

https://www.iqwig.de/de/methoden/methodenpapier.3020.html

# Bayesian methods in HTA



## Applications in clinical trials:

- Sample size calculation
- Dose-response experiments
- Monitoring of clinical trials
- Use of historical controls
- …

(Spiegelhalter & Freedman, 1994; Ashby, 2006)

# Bayesian methods in HTA



## Evidence synthesis:

- Pairwise meta-analysis
- Network meta-analysis
- Meta-regression
- Multi-level models

## Health economic models:

- Health economic decision models with parameter uncertainty
- Probabilistic methods for Bayesian networks

# Bayesian methods in IQWiG reports

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## Use of frequentist methods:

- Usual methods for parameter estimation and significance testing
- Pairwise meta-analysis, meta-regression

## Use of Bayesian methods:

- Network meta-analysis
- Reason:
  The first complex methods for network meta-analysis were developed in a Bayesian framework (Lu & Ades, 2004)

# Example: G09-01: Antidepressants

- Health economic evaluation of venlafaxine, duloxetine, bupropion, and mirtazapine compared to further prescribable pharmaceutical treatments
- Markov model was used for health economic evaluation
- Effect estimates of meta-analyses, indirect comparisons (Bucher method) and network meta-analyses were used as input for the Markov model
- For network meta-analysis Bayesian methods using MCMC and uninformative prior distributions were applied (Sturtz & Bender, 2012)
- Reason: The frequentist methods for network meta-analyses available at this time could **not** deal with multi-arm trials

# Example: A16-70: Rheumathoid arthritis

- Benefit assessment of biotechnologically produced drugs for the treatment of rheumatoid arthritis
- Comparison of 9 drugs
- Network meta-analysis
- Application of R package `netmeta` (Schwarzer et al., 2015)
- Use of frequentist methods now available (even for multi-arm trials)
- Simulation study demonstrated slightly better results for `netmeta` compared to Bayesian methods (Kiefer, 2015)
- No (arbitrary) choice of prior distributions required

# Use of Bayesian methods in IQWiG ?



- For network meta-analysis Bayesian methods no longer required
- Reason:
  Application of R package `netmeta`
- No application of Bayesian health economic models
- Reason:
  Currently no commission for health economic evaluations by the Joint Federal Committee

→ **No room for Bayesian methods in IQWiG?**

# Use of Bayesian methods in IQWiG ?



Bayesian methods still play a role:

- For network meta-analysis Bayesian methods no longer required, but nevertheless a valid option (at least for sensitivity analyses etc.)
- **Bayesian methods may play a major role for meta-analyses with very few trials in the future**

# Meta-analyses with very few studies



## Situation

- Fixed-effect (FE) model
  - Assumption: No true heterogeneity
- Random-effects (RE) model
  - Assumption: True heterogeneity (not too large)
  - DerSimonian & Laird (DSL) method (DerSimonian & Laird, 1986)
  - DSL ignores estimation uncertainty of $\tau$ (Veroniki et al., 2018)
  - A number of improved methods available
  - Knapp-Hartung (KH) method recommended (Veroniki et al., 2018)
  - Problem:

    In the case of very few studies $\tau$ cannot be estimated reliably

→ KH method over-conservative in the case of very few (2-4) studies

# Meta-analyses with very few studies



## Bayesian methods

- Bayesian methodology allows the inclusion of prior knowledge about the heterogeneity parameter in the form of (weakly) informative prior distributions (Friede et al., 2017)
- Compromise between over-confident FE meta-analysis and over-conservative RE meta-analysis based upon KH method ?
- Reliable information on the prior distribution of the unknown parameters is required
- It may be possible to use empirical data from the *Cochrane Database of Systematic Reviews* (Turner et al., 2015; Rhodes et al., 2015)
- Alternative: Use of expert beliefs (Ren et al., 2018)

## Bayesian methods

- However, it cannot be expected that a clear-cut choice for reliable prior information is available for all intervention types and all medical disciplines
- For binary data, use of half-normal priors with scale 0.5 and 1 for $\tau$ suggested (Friede et al., 2017)
- Even if these values are adequate, a decision is required which of these priors should be used
- A general scientific agreement is required which distribution for the heterogeneity parameter is valid for which situation

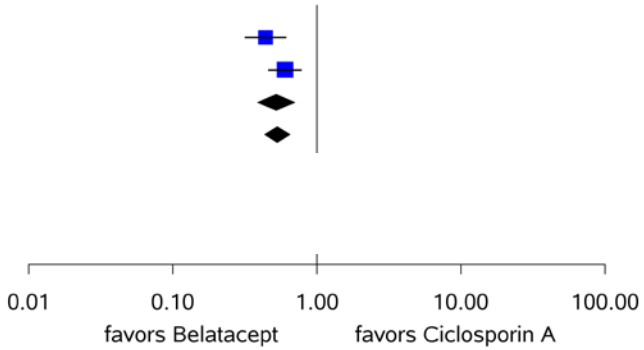
# Example

## Belatacept after kidney transplant (2 significant studies)

- Belatacept vs ciclosporin A for prophylaxis of graft rejection in adults receiving a renal transplant (IQWiG report A15-25)
- Endpoint "renal insufficiency in chronic kidney disease stage 4/5"

Figure 1
Belatacept vs. Ciclosporin A
Renal insufficiency in chronic kidney disease

| Study | log(HR) | SE | HR (95% CI) | weight (DSL) | HR | 95% CI |
|---|---|---|---|---|---|---|
| BENEFIT | -0.82 | 0.17 | | 44.6 | 0.44 | [0.32, 0.61] |
| BENEFIT-EXT | -0.51 | 0.13 | | 55.4 | 0.60 | [0.46, 0.78] |
| DSL | | | | 100.0 | 0.52 | [0.39, 0.71] |
| CE IV | | | | | 0.53 | [0.43, 0.65] |
| KH | | | | | 0.52 | [0.07, 3.71] |
| B-HN(0.5) | | | | | 0.53 | [0.27, 0.98] |
| B-HN(1.0) | | | | | 0.52 | [0.17, 1.52] |




Heterogeneity: Q=2.06, df=1, p=0.151, $I^2$=51.5%
Overall effect: Z Score=-4.21, p<0.001, Tau=0.157

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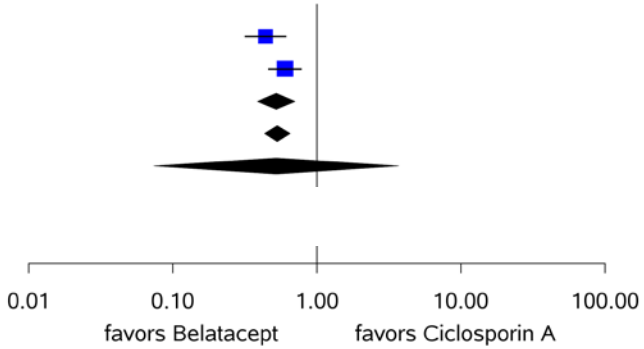


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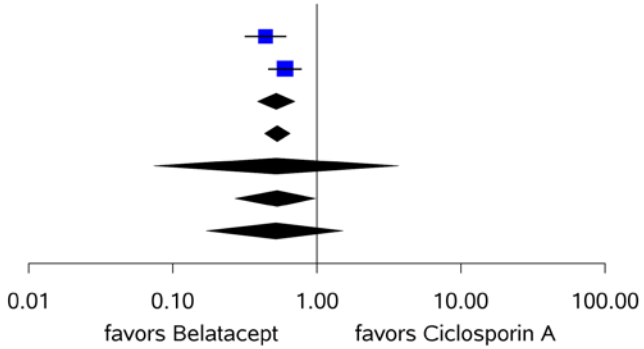


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→ 1) KH over-conservative; decision of no added benefit critical
2) Bayesian approach requires the decision of the "right" prior

# Discussion

- No satisfactory standard method is currently available to perform meta-analyses in the case of very few studies
- FE model in practice possible, but has limitations (over-confident in the case of true heterogeneity)
- In general, whenever heterogeneity cannot be excluded, the FE model should not be used
- However, in situations with only 1 single study, results of this study are interpreted and conclusions are made for the considered population
- In the case of 2 or more studies we can technically investigate heterogeneity and we try to assess heterogeneity even if heterogeneity cannot reliably estimated
- Thus, in the situation with very few studies, the simple FE model should be applied more frequently (Bender et al., 2018)

# Conclusion

- Bayesian methods with informative priors may be a valid compromise between over-confident FE meta-analysis and over-conservative RE meta-analysis
- A general scientific agreement is required which prior distribution for the heterogeneity parameter is valid for which situation
- **Can this workshop be a starting point to reach such an agreement ?**

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