On the road to clinical extrapolation

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Application of Bayesian methodology

- Often proposed for situations with

  limited options to recruit patients into studies (rare disease, pediatric trials)

  or potential limited need (extrapolation from adult to pediatric indications)
- Use of „expert opinion“ to interlink pathophysiological or pharmacological plausibility assumptions with the response parameter
- In rare disease some pre-specified expert opinion may be the only option to reduce the burden of evidence needed for “proof” of efficacy
- In extrapolation, however, data in adults are available to inform about prior knowledge regarding a drug in a certain context (e.g. immunosuppression in organ transplantation)

Bayesian extrapolation (and regulatory context)

Tradition in drug regulation:

- Self standing data-based decision making
- Primary use of own data (class is of secondary interest)
- Pre-specified decision making process

Thus:

- In case data are available, preference is given to data (and not to expert opinion)
- In case information is borrowed, then this should be primarily “own” information
- Conclusions should be non-trivial (e.g. the prior completely determines the evaluation of the new experiment)

Paediatric extrapolation

In contrast to other situations:

- Available data have been sufficient for licensing a new drug
- PK/PD and mechanism of action are usually well understood
- PK/PD in paediatric patients available (or can be generated “easily”)

Why then clinical data in paediatric patients?

- Low belief that similar PK/PD leads to the same clinical efficacy
- No reliable PD endpoint
- Puzzling outcome in previous steps of the extrapolation exercise

Drug regulation clarifies the need-to-knows and not the nice-to-knows. To have “at least some paediatric data” would be neither ethical nor scientific as a motivation to do a human experiment.

Regulatory question

Going for an extrapolation exercise assumes an agreement that there is no need for formal (self-standing) proof of efficacy in the paediatric population. Instead, the following questions need to be addressed:

A. Which paediatric experiment is needed to detect with good probability relevant deviations from adult expectations regarding the treatment effect?

B. How to define and assess “relevant deviations”?

To be presented here:

Play-games with differing amounts of information (e.g. a lot of information in adults and only a few children)

Play-game: EVR case-study

Adult studies in de novo kidney transplants with EVR (NIM(log(OR)): 0.54)

study	EVR events/treated	MPA events/treated	Log(OR 95% CI P-value
B201 Vitko 2004	58/194 (29.9%)	61/196 (31.1%)	-0.05 (-0.48, 0.38) 0.793
B251 Lorber 2005	48/193 (24.9%)	54/196 (27.6%)	-0.13 (-0.58, 0.32) 0.548
A2309 Tedesco 2010	70/277 (25.3%)	67/277 (24.2%)	0.06 (-0.33, 0.45) 0.844
Meta-Analysis (FEM & REM)			-0.035 (-0.28, 0.21) 0.776

Studies investigated different comparators, but demonstration of non-inferiority was felt relevant in all instances.

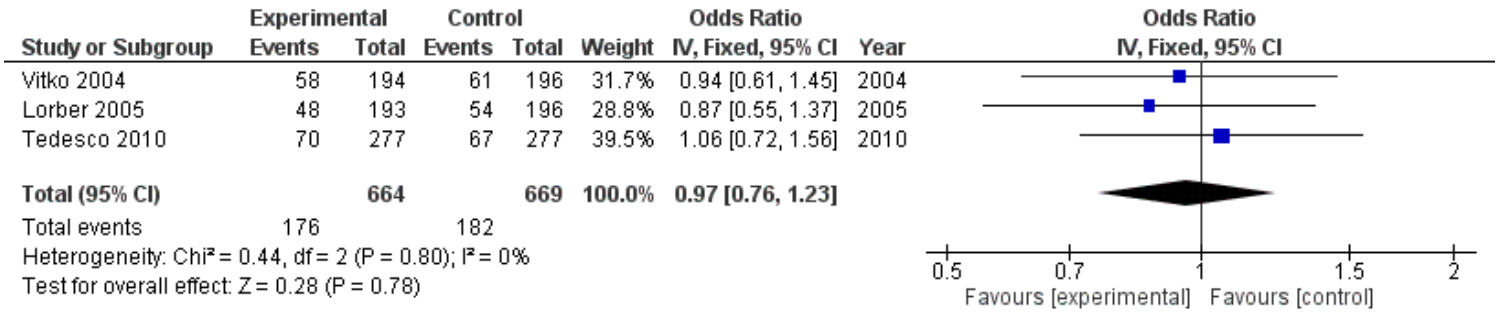
B201 (Vitko 2004): ***CS+CsA(s)+EVR vs. CS+CsA(s)+MMF,***
B251 (Lorber 2005): ***CS+CsA(s)+EVR vs. CS+CsA(s)+MMF,***
A2309 (Tedesco 2010): ***CS+B+CsA(r)+EVR vs. CS+B+CsA(s)+MPA.***

Pay-game: EVR case-study

Aim: extrapolation to the paediatric population with one clinical study

Investigation of two different scenarios:

study	EVR events/treated	MPA events/treated	log (OR) 95% CI P-value
Scenario 1	16/53 30.2%	16/53 30.2%	0.00 (-0.83; 0.83) 1.00
Scenario 2	22/53 41.5%	16/53 30.2%	0.50 (-0.31; 1.30) 0.33



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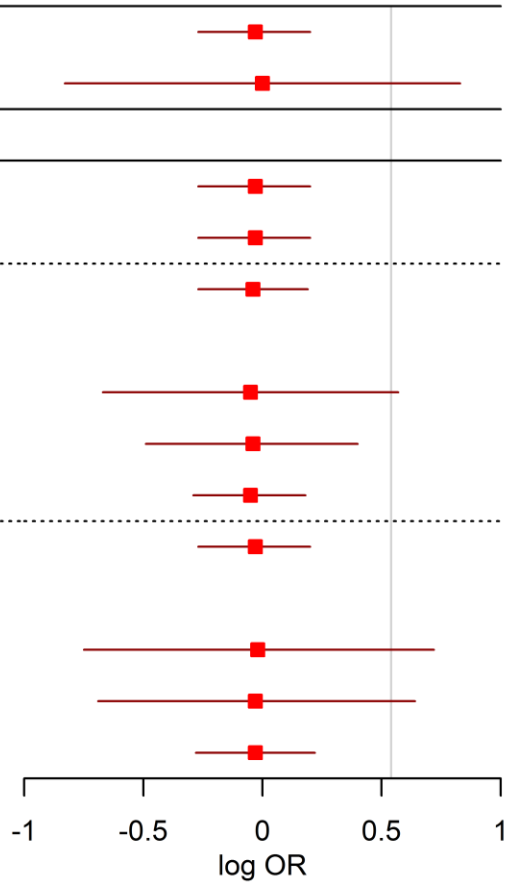
Approaches to a summary evaluation of individual sources of information

- **Frequentist Meta-Analysis**
  - Joint analysis of existing and new trials (eventually looking into heterogeneity) in a fixed (FEM) or a random (REM) effects model
- **Bayesian Meta-Analysis**
  - Joint analysis of existing and new trial in a FEM or a REM (Smith et al., 1995)
- **Bayesian meta-analytic predictive approach**
  - Analysis of a new trial „in light of“al ready existing trials in a FEM or a REM (Viele et al., 2014 and Spiegelhalter et al., 2004)

Results with Scenario 1 (assumed homogeneity)

Study		log OR	
adult MA		-0.03	
Scenario 1		0	
Analysis method	**Prior**	**log OR**	**Heterogeneity**
F FE MA		-0.03	q=0.44, $\hat{\tau}^2$= 0.00
F RE MA		-0.03	
B FE MA		-0.04	
B RE MA			
prior: E(τ^2) = 0.33		-0.05	$\hat{\tau}^2$= 0.31
prior: E(τ^2) = 0.14		-0.04	$\hat{\tau}^2$= 0.14
prior: E(τ^2) = 0.001		-0.05	$\hat{\tau}^2$= 0.001
B FE MAP	adult	-0.03	
B RE MAP			
prior: E(τ^2) = 0.33	adult	-0.02	$\hat{\tau}^2$= 0.42
prior: E(τ^2) = 0.14	adult	-0.03	$\hat{\tau}^2$= 0.16
prior: E(τ^2) = 0.001	adult	-0.03	$\hat{\tau}^2$= 0.001



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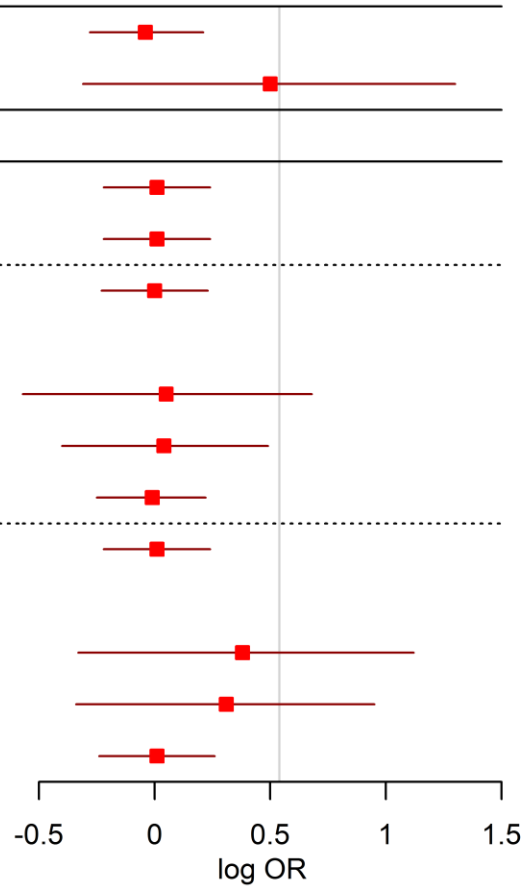
Results with Scenario 2 (log OR = 0.50, at the margin)

Study		log OR	
adult MA		-0.04	
Scenario 2		0.5	
Analysis method	**Prior**	**log OR**	**Heterogeneity**
F FE MA		0.01	q=0.44, $\hat{\tau}^2$= 0.00
F RE MA		0.01	
B FE MA		0	
B RE MA			
prior: E(τ^2) = 0.33		0.05	$\hat{\tau}^2$= 0.32
prior: E(τ^2) = 0.14		0.04	$\hat{\tau}^2$= 0.15
prior: E(τ^2) = 0.001		-0.01	$\hat{\tau}^2$= 0.001
B FE MAP	adult	0.01	
B RE MAP			
prior: E(τ^2) = 0.33	adult	0.38	$\hat{\tau}^2$= 0.43
prior: E(τ^2) = 0.14	adult	0.31	$\hat{\tau}^2$= 0.16
prior: E(τ^2) = 0.001	adult	0.01	$\hat{\tau}^2$= 0.001



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Assessment of the exemplary analyses

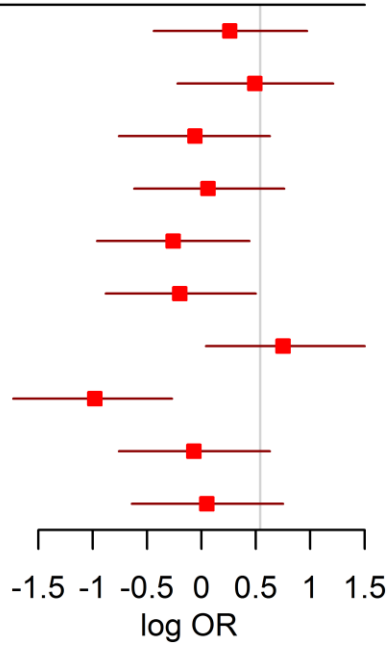
Many approaches and …

- … many different conclusions about the same data possible
- If meta-analysis is used as a tool to arrive at an overall conclusion, no difference between a frequentist approach or a Bayesian approach can be detected: actually summary estimates will always be dominated by adult data.
- Using the predictive approach might allow that the pediatric data stand against the adult data (in case a prior is chosen that will allow for heterogeneity), however then even in case of homogeneity nothing can be concluded with the current sample-size.
- If heterogeneity is restricted, the impact of the adult data is increased (similar to frequentist MA).
- Precise pre-specification of the assumptions is required / recommended.

“Simulation” to reduce optimism

Some random draws under the assumption of homogeneity;

Analysis method	prior	log OR	est. Heterogeneity
B RE MA prior: $E(\tau^2) = 0.33$	adult	0.26	0.43
B RE MA prior: $E(\tau^2) = 0.33$	adult	0.49	0.44
B RE MA prior: $E(\tau^2) = 0.33$	adult	-0.06	0.41
B RE MA prior: $E(\tau^2) = 0.33$	adult	0.06	0.42
B RE MA prior: $E(\tau^2) = 0.33$	adult	-0.26	0.42
B RE MA prior: $E(\tau^2) = 0.33$	adult	-0.2	0.41
B RE MA prior: $E(\tau^2) = 0.33$	adult	0.75	0.48
B RE MA prior: $E(\tau^2) = 0.33$	adult	-0.98	0.5
B RE MA prior: $E(\tau^2) = 0.33$	adult	-0.07	0.41
B RE MA prior: $E(\tau^2) = 0.33$	adult	0.05	0.42



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Summary and conclusions

Extrapolation ↔ self standing evidence

- Data-based extrapolation is possible but…
- … all methods implicitly reduce the amount of data needed for a formal decision making process if the focus lays only on the final estimate (and CI)
- Clinical extrapolation could be seen as a descriptive exercise (w/o need for confirmatory decision making), but how then to justify sample-size?
- One may decide that no pediatric clinical trial is needed (PK or PK/PD is sufficient), but if one is done, it needs to have an objective to be achieved.

Summary and conclusions

Idea exists that extrapolation is an iterative process
(model → collect data → check fit → evaluate → eventually redo)

- This may be feasible in PK/PD in general, but may not be true in the field of extrapolation:
  - All knowledge has been used-up for the best prediction of pediatric outcome.
  - If then reality doesn't fit our plans – isn't this evidence that extrapolation from adult to pediatric is (too) limited / not possible?
  - Re-do in the world of clinical trials would be extremely costly

Summary and conclusions

What could be done?

- A lot of different methods (e.g. relax T1E, increase NI-margin, meta-analyze, pep-up your control group or just omit it).
- Methodological problems exist, but not in the field of whether Bayesian or Frequentist statistics are more appropriate.
- It is more important to precisely define the research question and get the metrics clear to make maximum out of the fact that formal proof of efficacy in adults is already available.
- A check for consistency should be implemented/possible
- The value of confirmatory (pre-planned) decision making:
  - a chance to discuss the required amount of information upfront
  - avoid unethical / costly collection of data that is difficult to use

Summary and conclusions

Some recommendations open for discussion:

→ Avoiding “overweight” in the MA-approach with content-wise selection of adult patients (e.g. only use data from young adults to weigh in for the assessment of adolescent pediatric patients)

→ Be precise about the prior information and its possible impact

→ Change of emphasis from “Does it work?” towards “Is there evidence for differential effects?”

Thank you for your attention!

References

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