An extrapolation framework to specify requirements for drug development in children

Martin Posch

joint work with

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Clinical Trials in Small Populations
December 2, 2015, London

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Drugs and Biologics for the Pediatric Population

- For many years drugs and biologics were primarily evaluated in adults:
  - simpler
  - fewer ethical concerns
- Nevertheless, following regulatory approval for adults, off label use (with no clinical trials in children) was frequent.
- Often empirically selected lower doses based on the weight of the child were used.
- Potential exposure of children to unsafe or ineffective treatments (e.g., there maybe differences in metabolization).
- 2006 European Pediatric Regulation

EU Pediatric Regulation

Requirement: Paediatric Investigation Plan (PIP) for all new drugs & new indications of authorized drug or deferral or waiver

Objectives:

- high quality, ethical research into medicines for children
- increase availability of authorised medicines for children
- without subjecting children to unnecessary studies

The Paediatric Investigation Plan (PIP)

- Specifies a plan for pharmaceutical and clinical development to support the authorisation of a drug for children
- At the end of phase I of adult development
- PIP proposed by the company and modified and agreed/declined by Paediatric Committee (PDCO) at the European Medicines Agency
- Later modifications possible if requested by the company
- Legally binding

EMA/PDCO/367243/2015
London, 14 August 2015

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver
EMEA-001461-PIP02-14

Scope of the application

Active substance(s):

Acotiamide

Condition(s):

Treatment of functional dyspepsia

Pharmaceutical form(s):

Coated tablet

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Zeria Pharmaceutical Co Ltd

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Zeria Pharmaceutical Co Ltd submitted for agreement to the European Medicines Agency on 7 November 2014 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 16 December 2014.

Supplementary information was provided by the applicant on 20 May 2015. The applicant proposed modifications to the paediatric investigation plan.

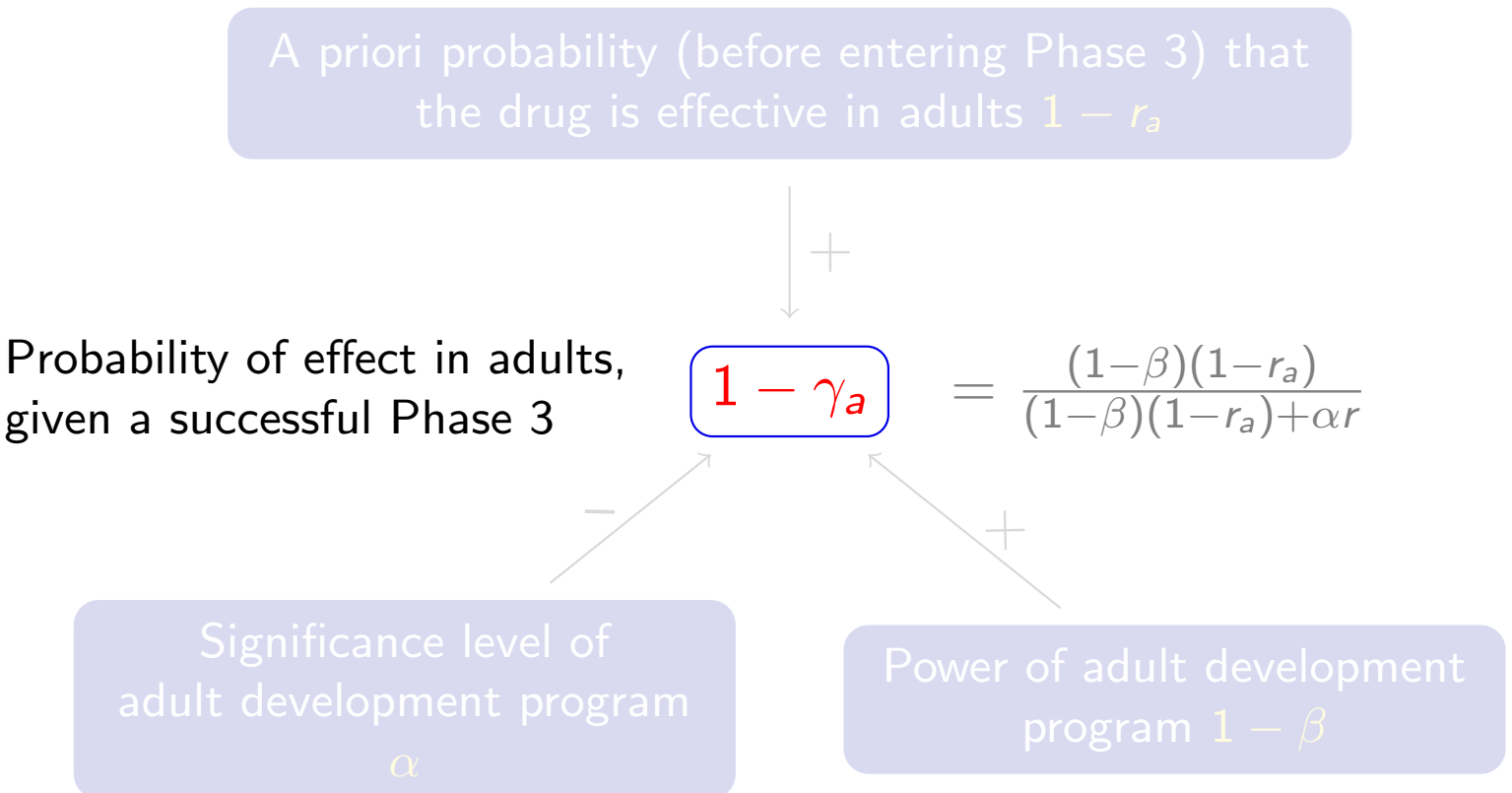
Requirements for the Paediatric Investigation Plan

- To which extent can results from adult trials be extrapolated to children?
- What additional information is required in the paediatric population?
- How do extrapolation assumptions impact on the requirements for the PIP?
- Under the assumption that the drug will be approved for adults (based on pivotal trials in adults) can we relax the standard significance level for pivotal trials in children?

At the time of approving the drug for children, our confidence in the efficacy of the drug in children should be not less than the confidence in the efficacy of the drug in adults.

Confidence in Efficacy in Adults

What is the probability that the drug is effective in adults, given a successful adult development program?



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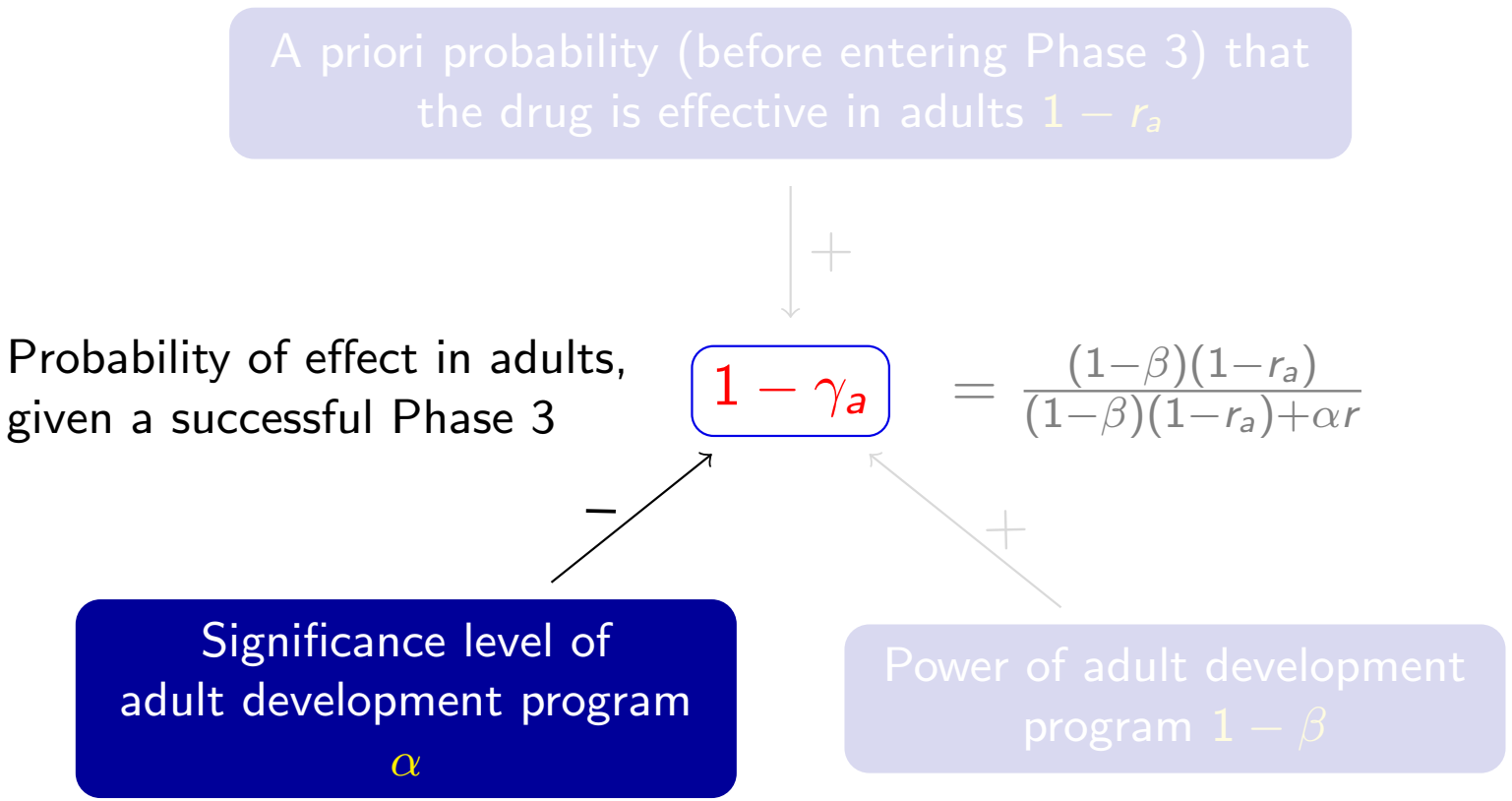

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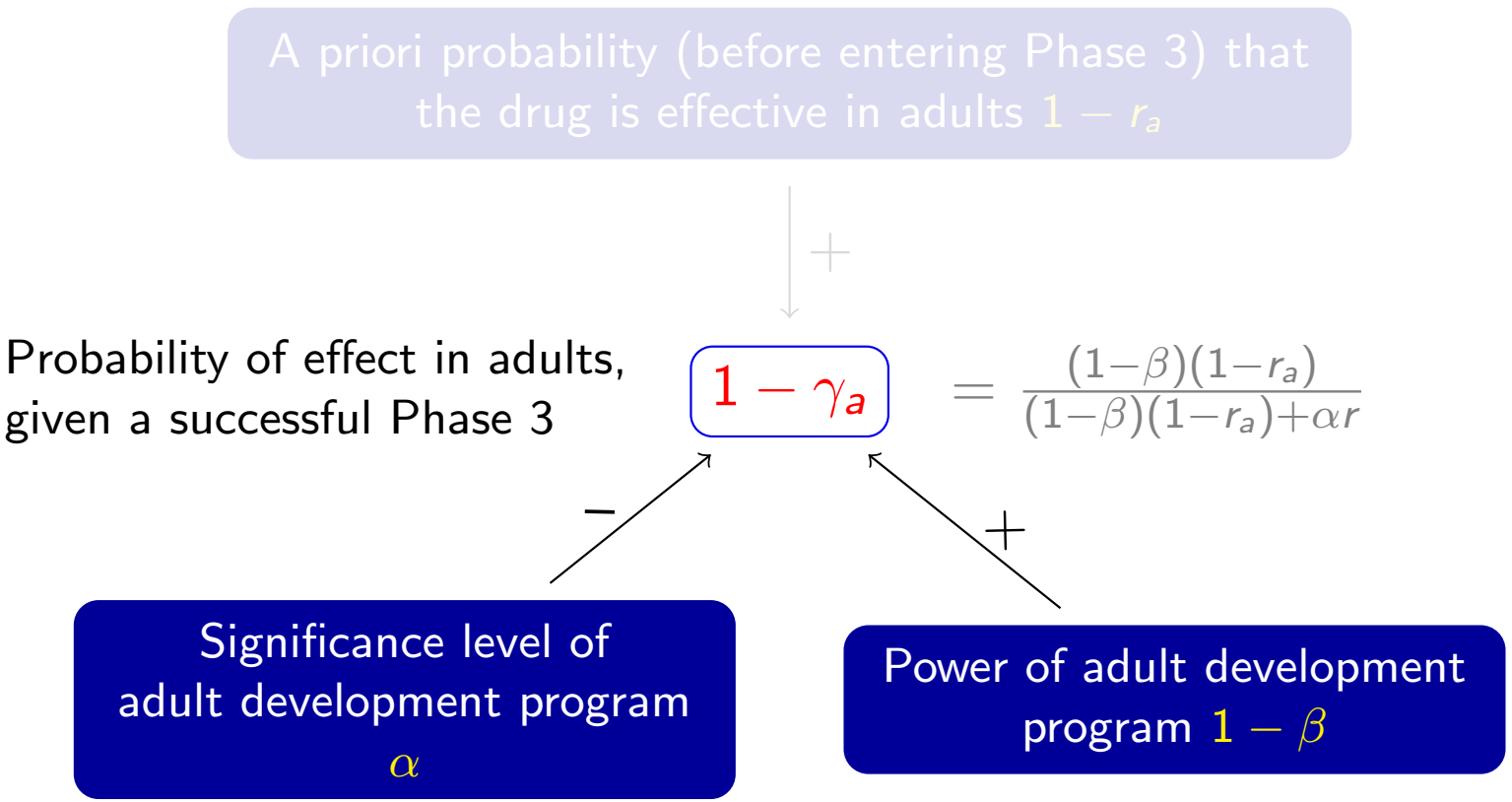

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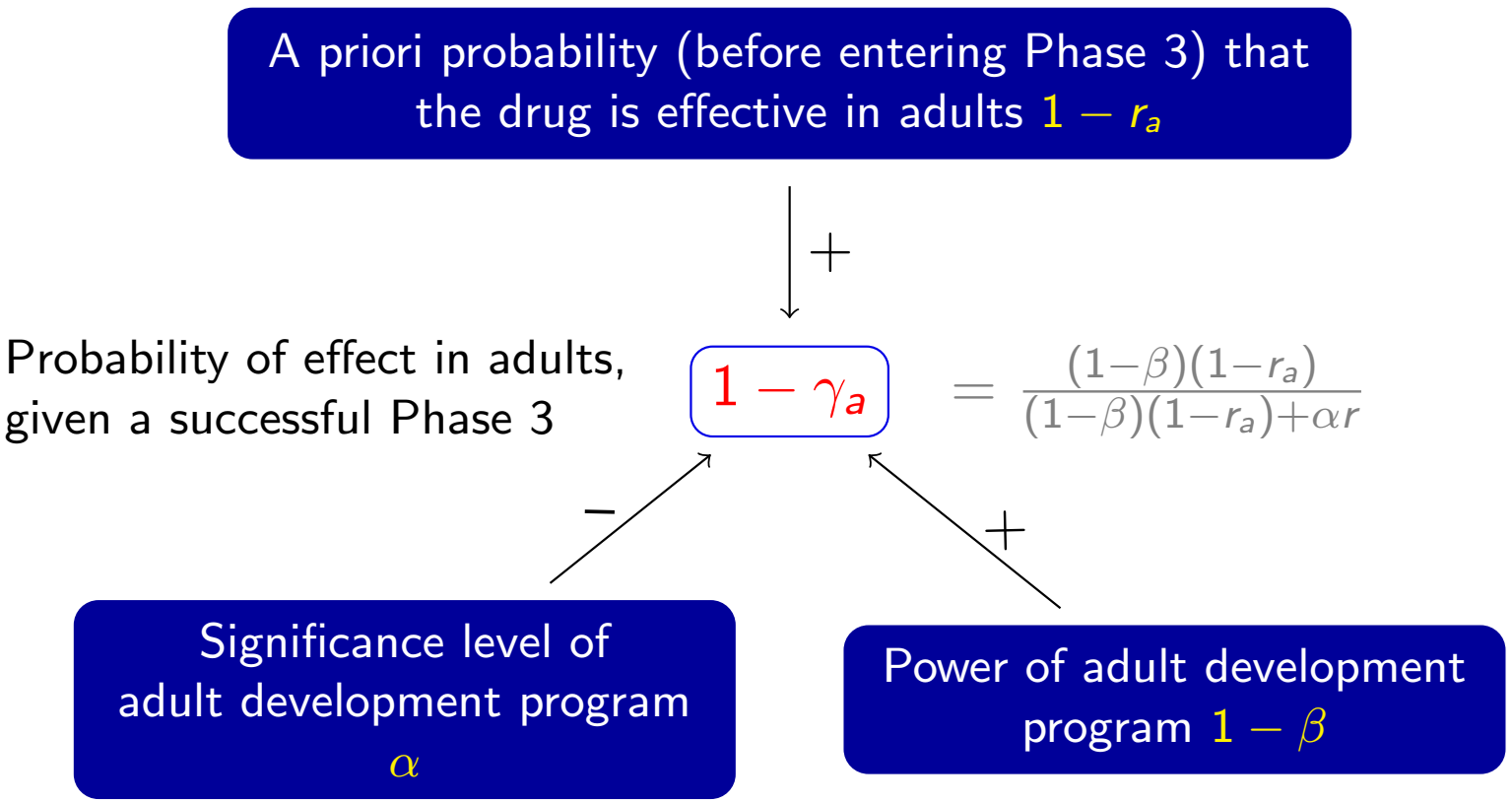

How to determine the prior probability for efficacy $1 - r_a$?

- Elicitation from expert knowledge
- Estimation from historic Phase 3 success rates

Estimation of $1 - r_a$ based on historic success rates

- In oncology, 40% of new compounds entering Phase 3 are proven to be effective.[1]
- Under the assumption that the success rate is based on developments with two pivotal trials at overall level 0.025^2 and power 80%

$$1 - r_a = 0.5$$

[1] Hay et al. Clinical development success rates for investigational drugs. Nature biotechnology 2014;

The confidence for efficacy in adults

Given a prior belief $1 - r_a = 0.5$ the confidence in efficacy conditional on a future successful adult development program is:

$1 - \gamma_a = 0.973$ if a single trial at level 0.025 and power 90% is performed

$1 - \gamma_a = 0.9992$ if two trials are performed such that the overall level is 0.025^2 and overall power is 80%.

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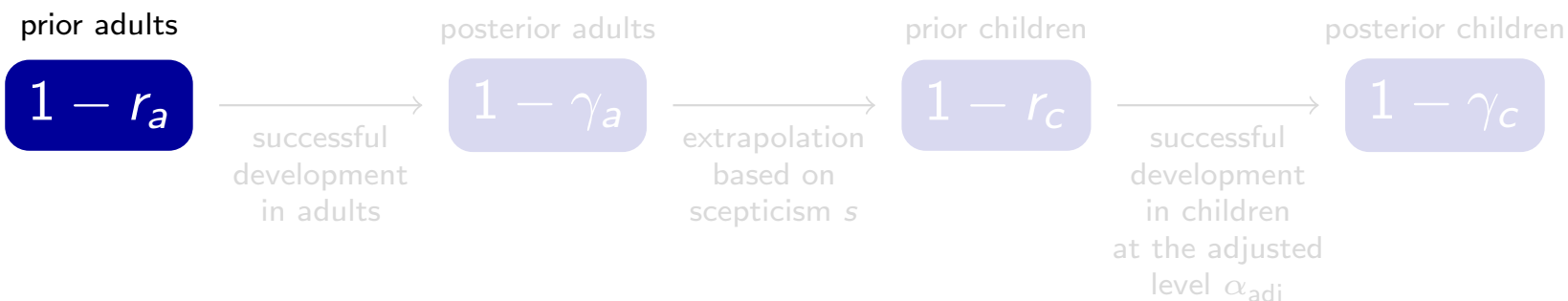

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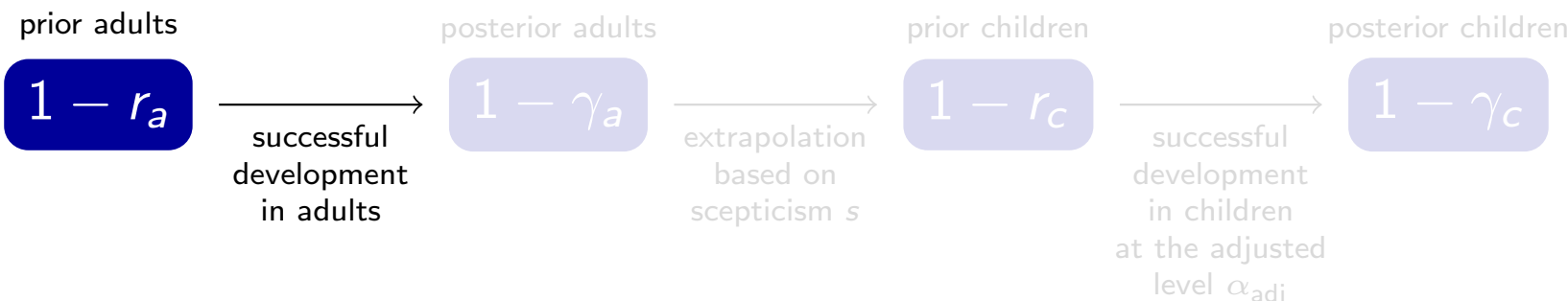

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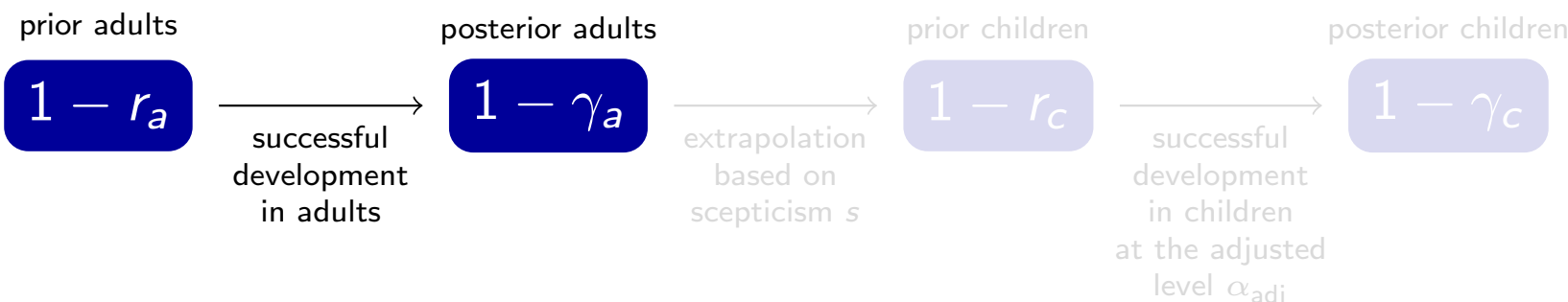


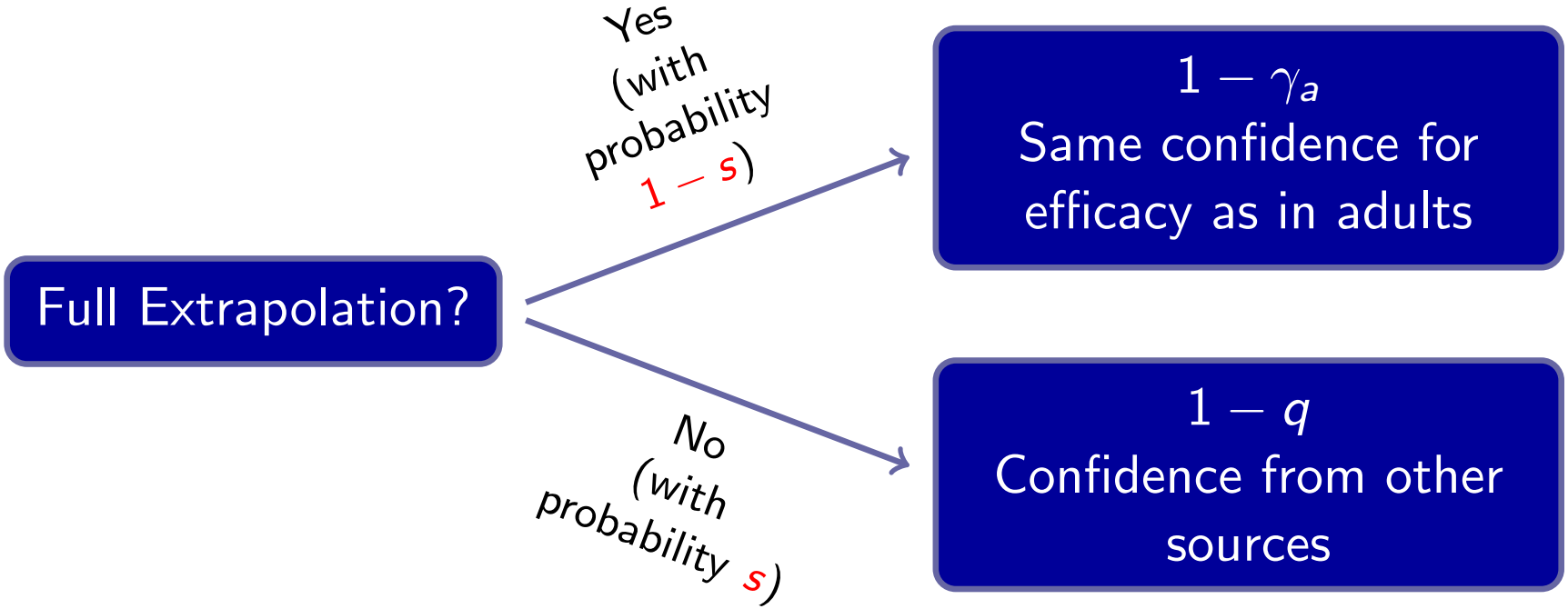
Extrapolation from Adults to Children

What is the confidence for efficacy in children conditional on a future successful drug development in adults?

- Let the Scepticism s denote the probability that efficacy in adults *cannot* be extrapolated to children.
  - With probability $1 - s$ the confidence in efficacy in adults directly transfers to efficacy in children.
  - With probability s extrapolation cannot be applied and the confidence for efficacy in children needs to rely on other sources.

Early Confidence for Efficacy in Children

. . . conditional on a future successful drug development in adults

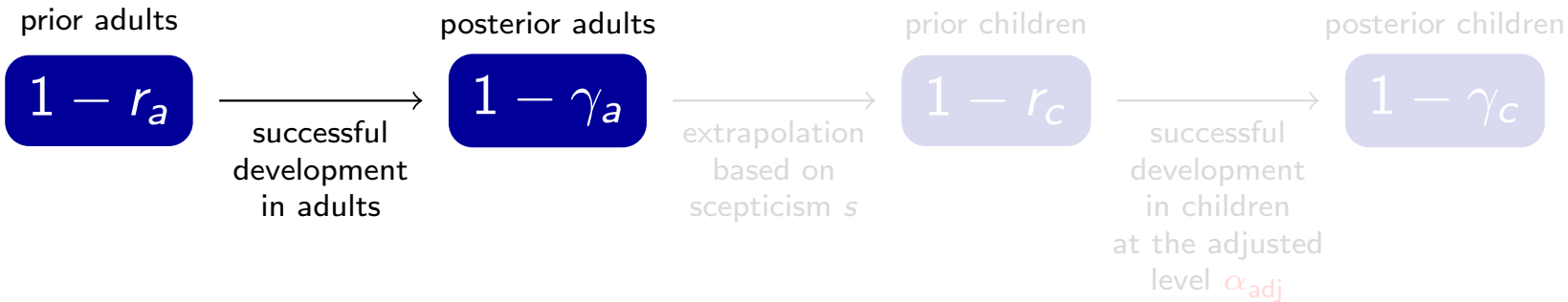


The overall early confidence for efficacy in children conditional on a future successful drug development in adults is

$$1 - r_c = (1-s)(1-\gamma_a) + s(1-q)$$

Conditional future confidence for efficacy in children

conditional on a successful drug development in children at level α_{adj}



Which significance level α_{adj} do we need to apply in children to achieve the same confidence (conditional on a positive paediatric development) for efficacy for the vulnerable paediatric population as for adults, s.t.

$$1 - \gamma_c = \frac{(1-\beta)(1-r_c)}{(1-\beta)(1-r_c) + \alpha_{\text{adj}} r_c} = 1 - \gamma_a \quad ?$$

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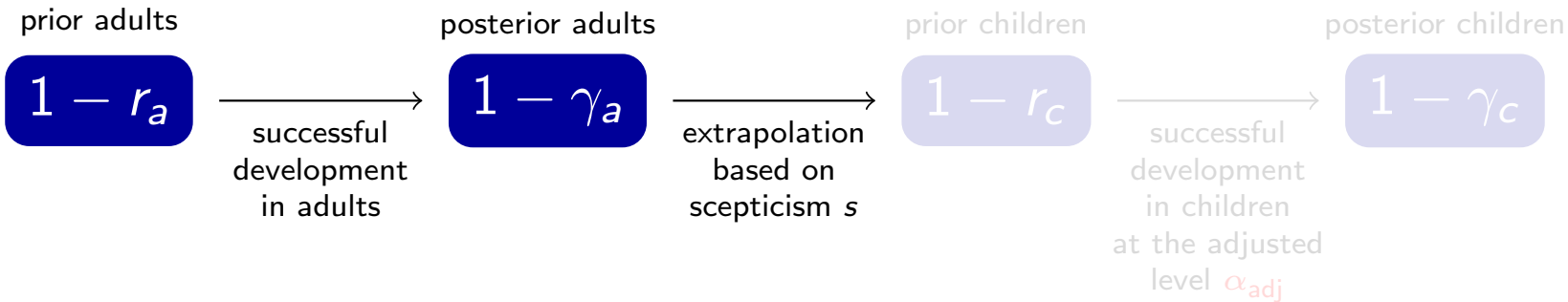

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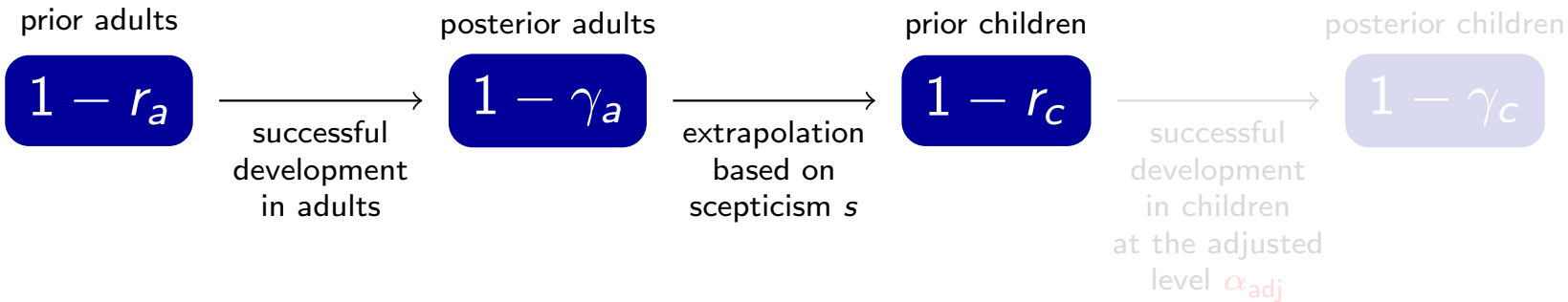

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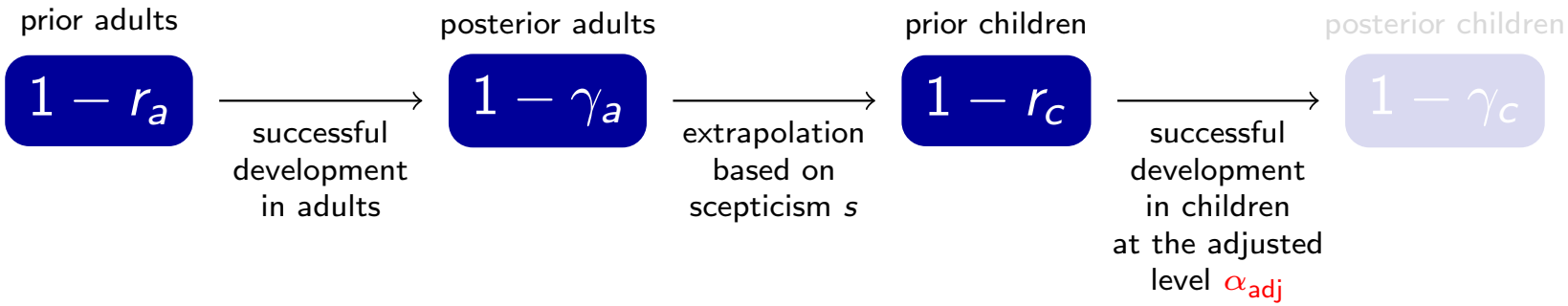

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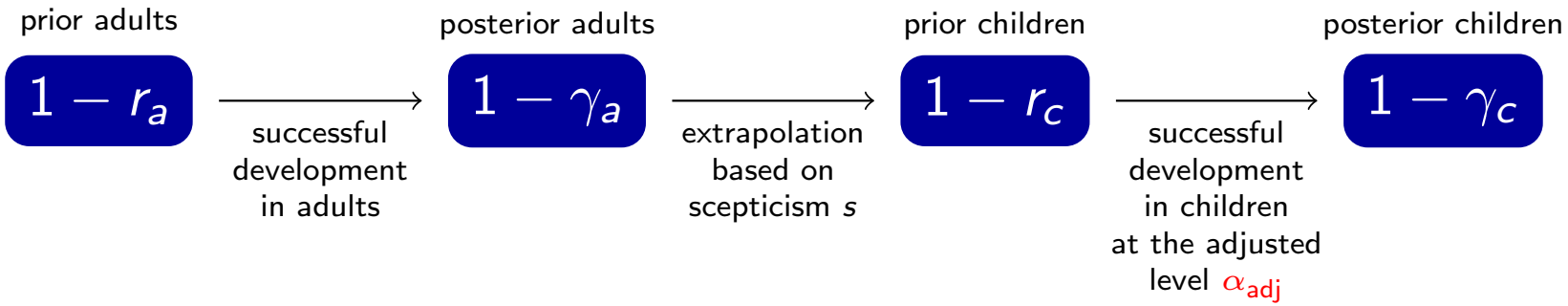

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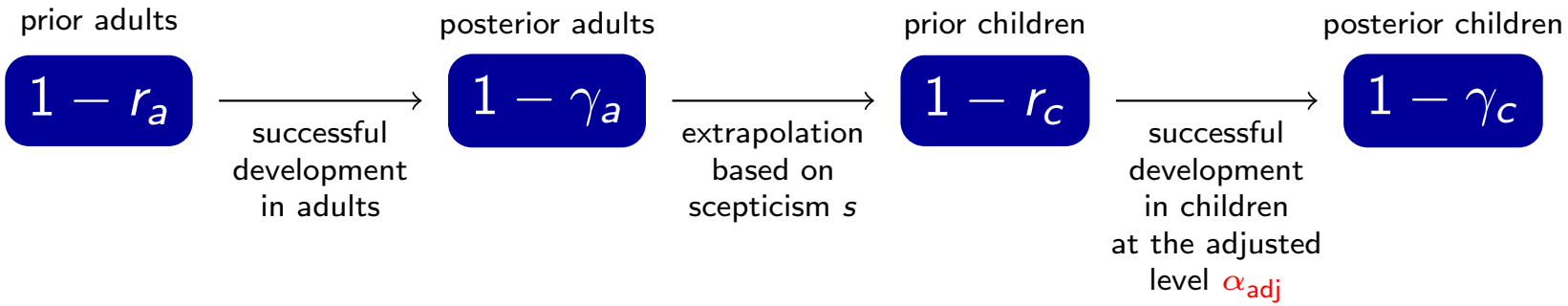

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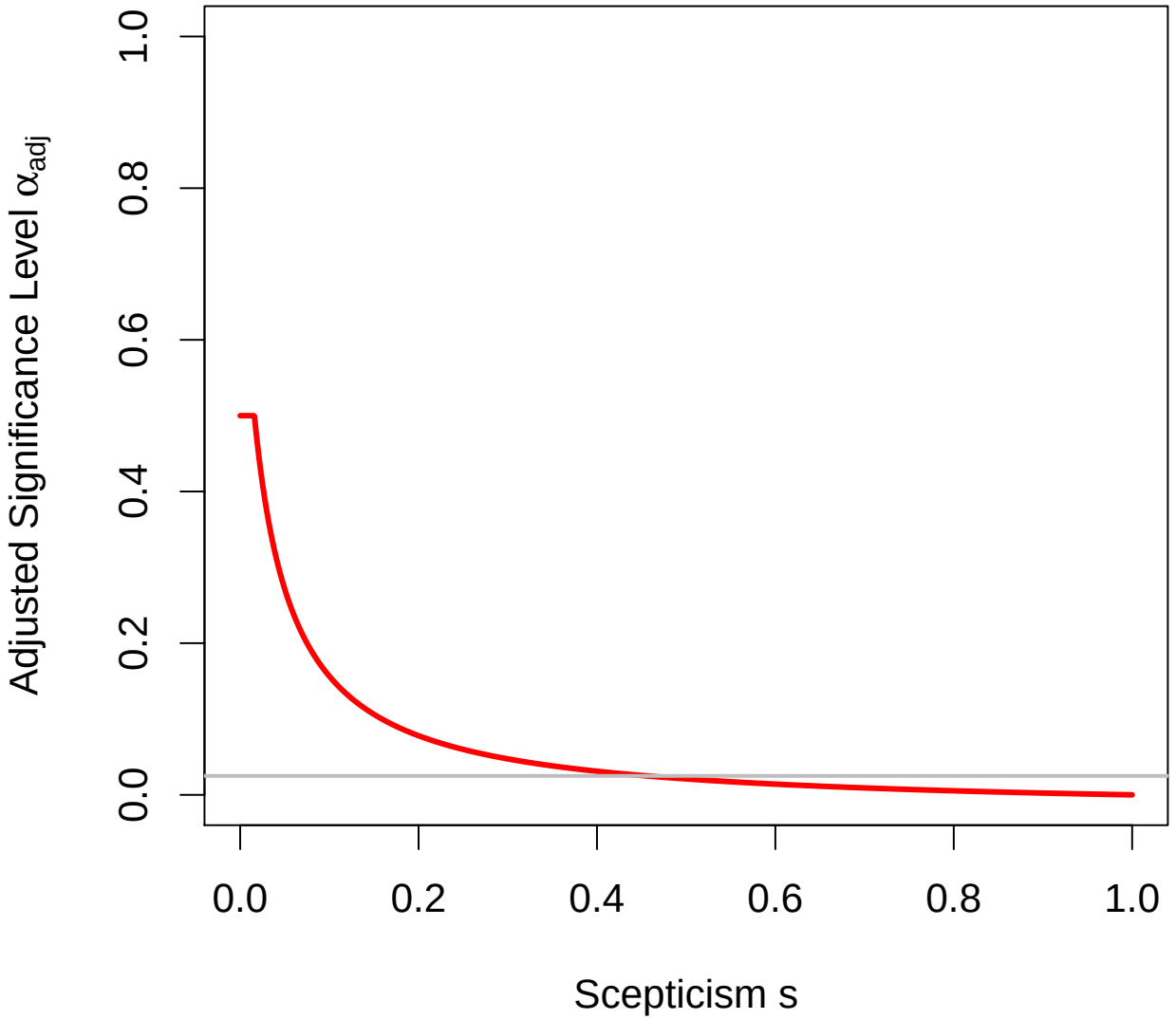

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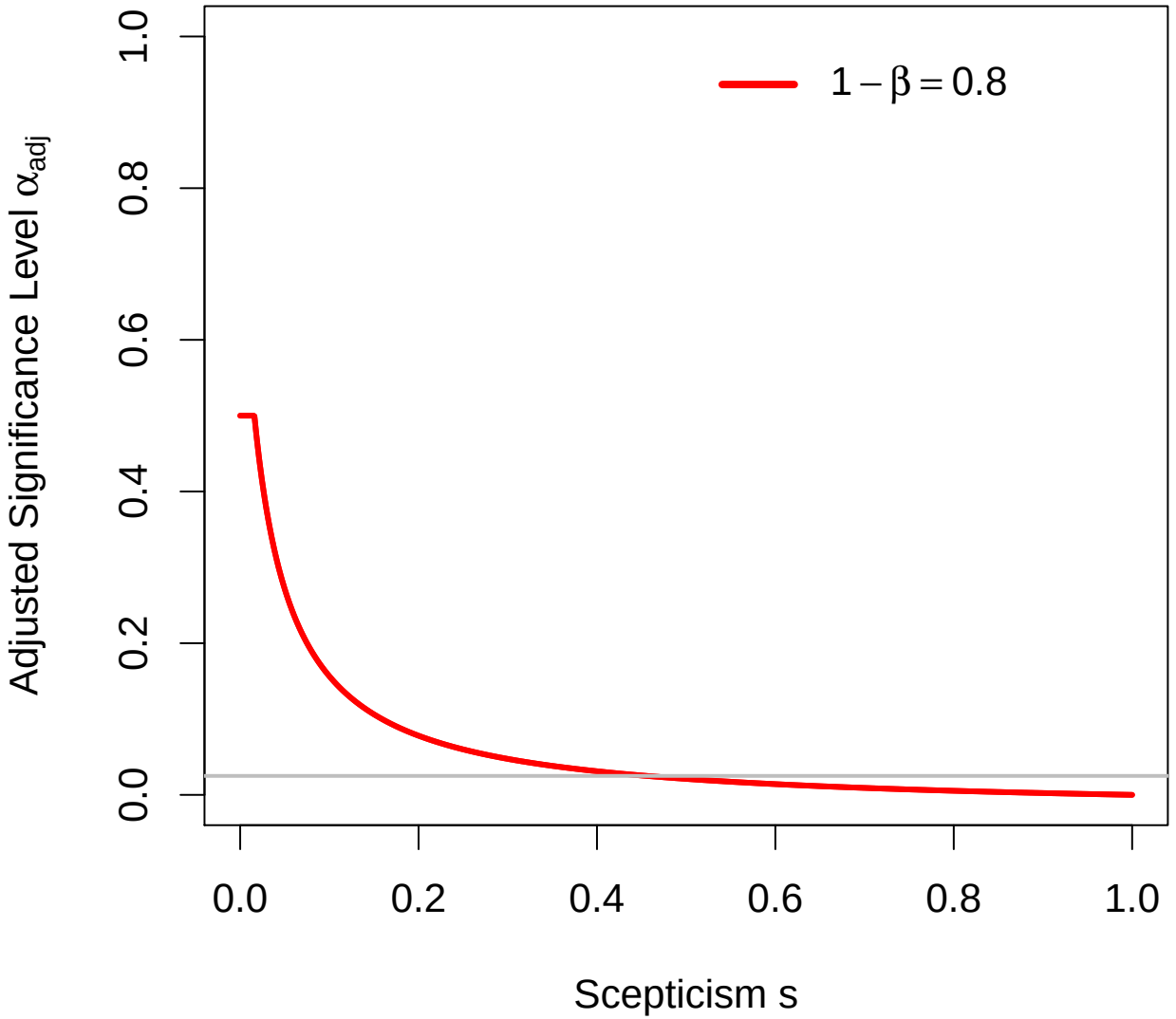

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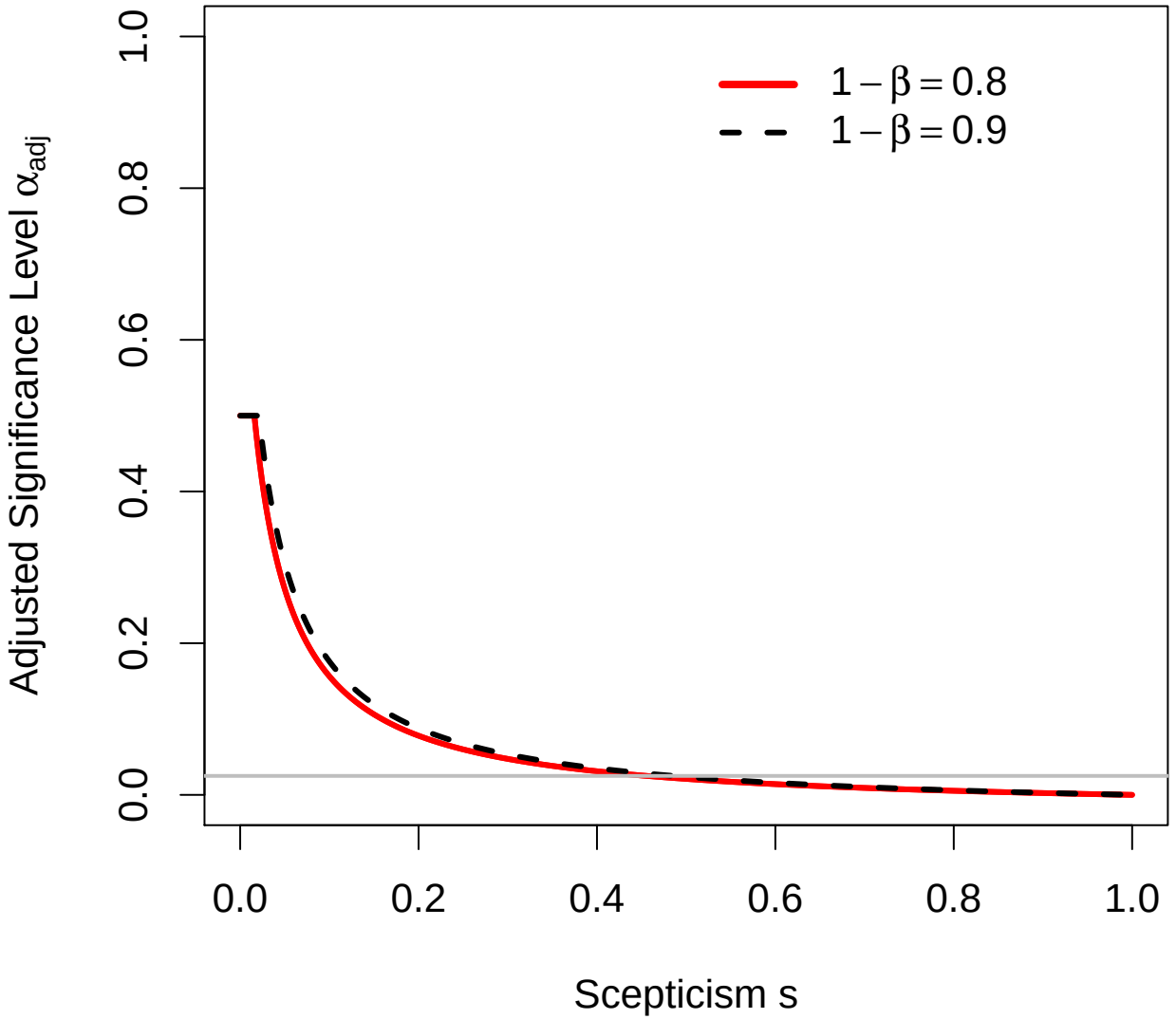

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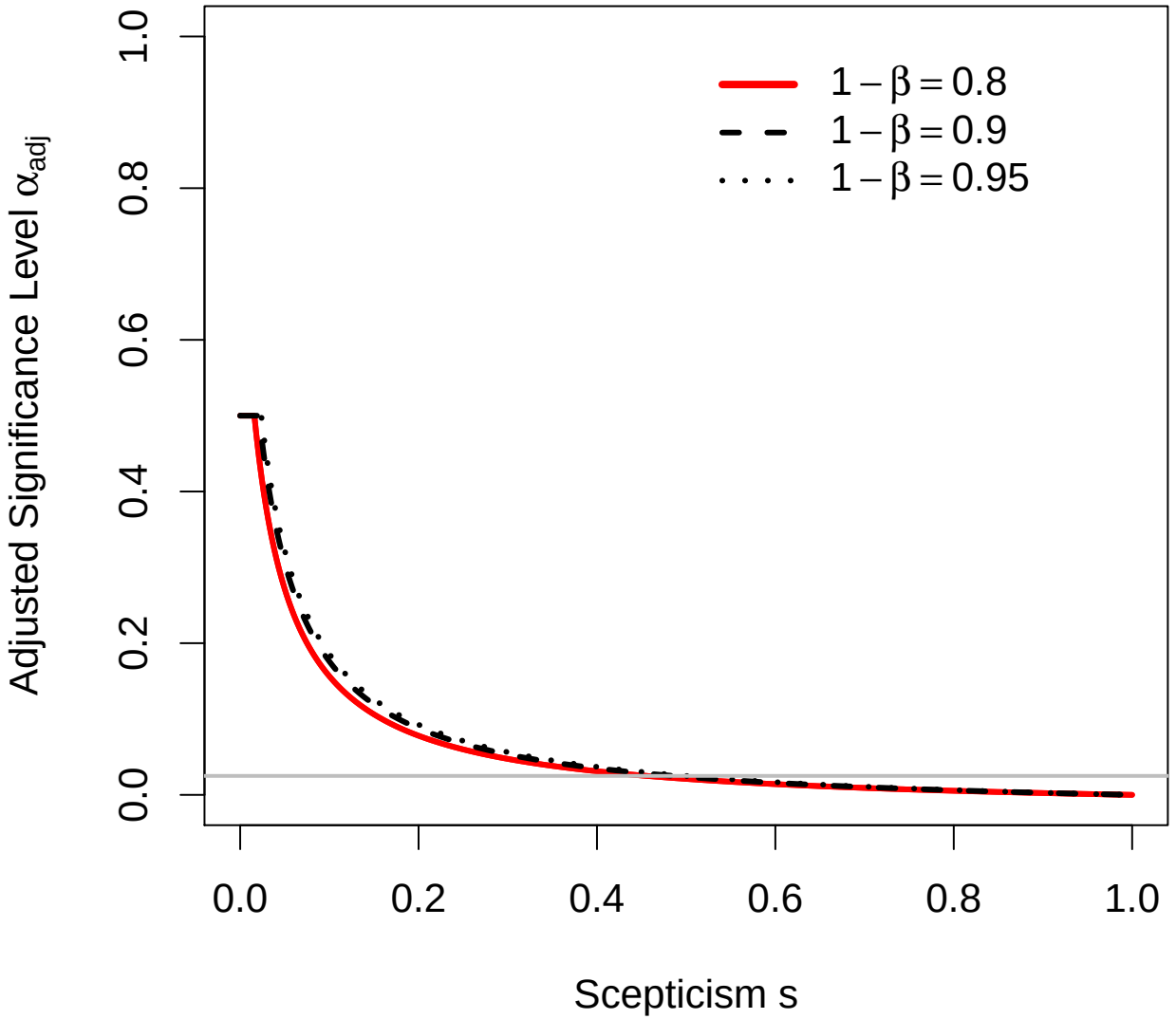

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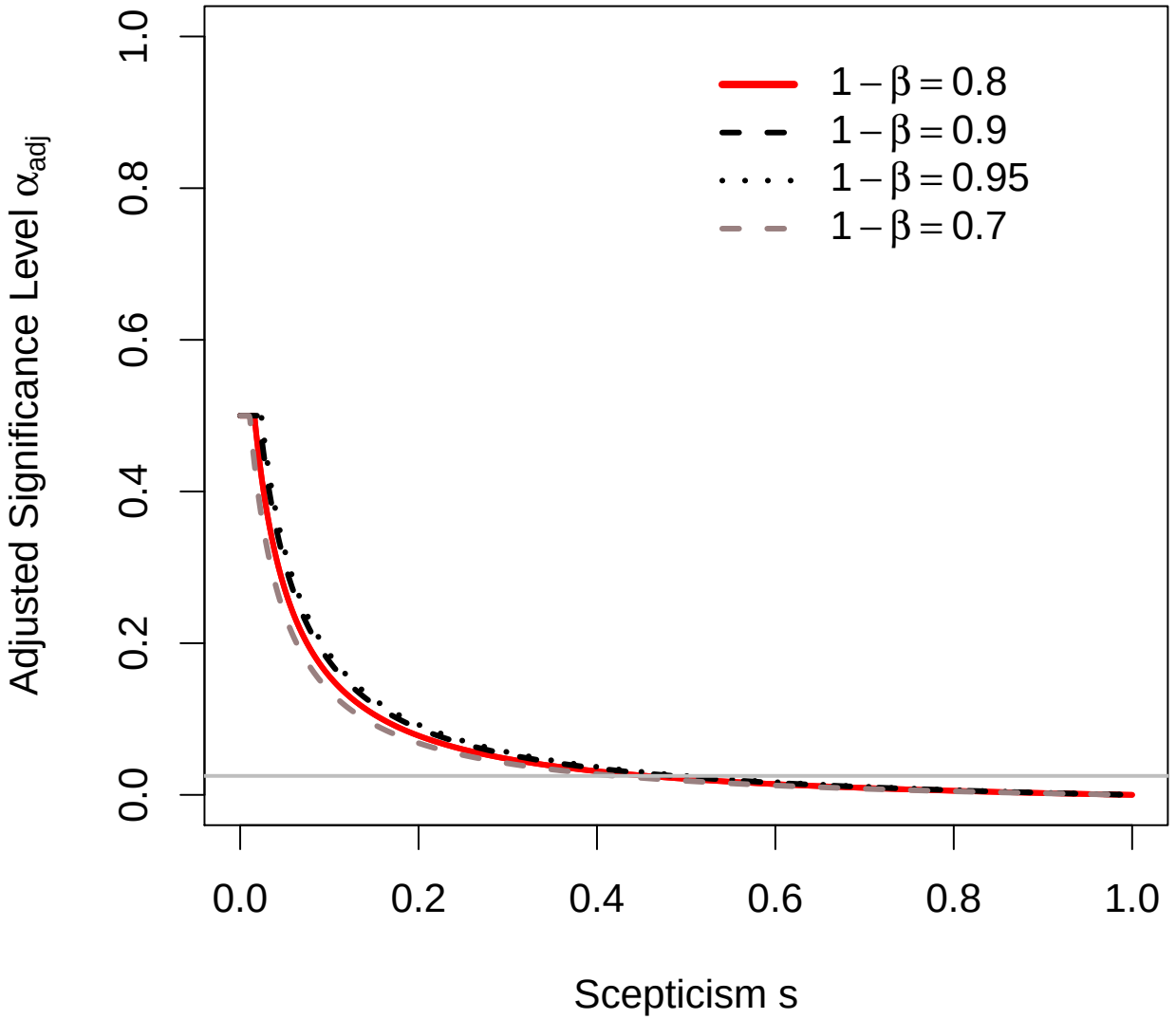

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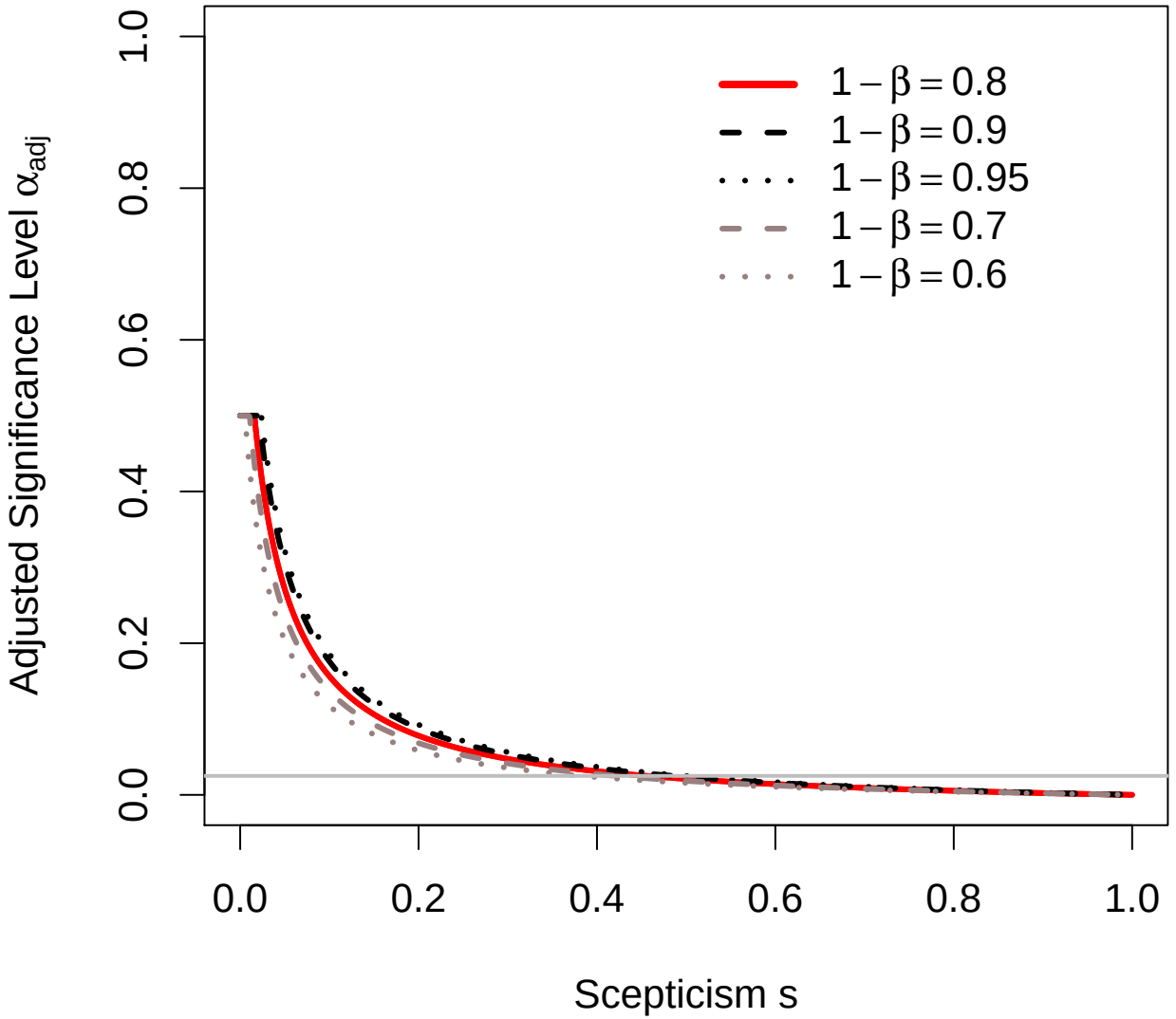

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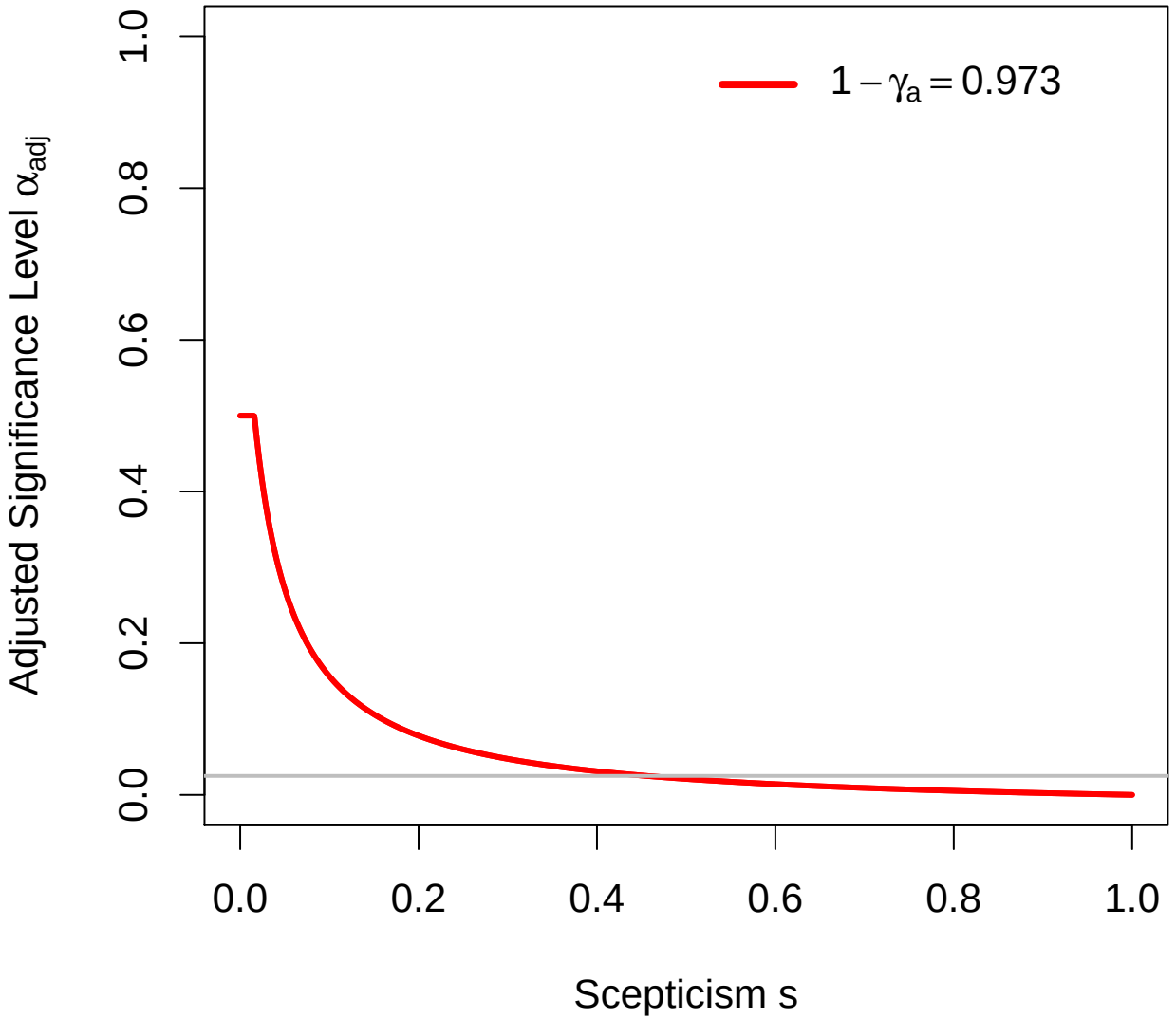

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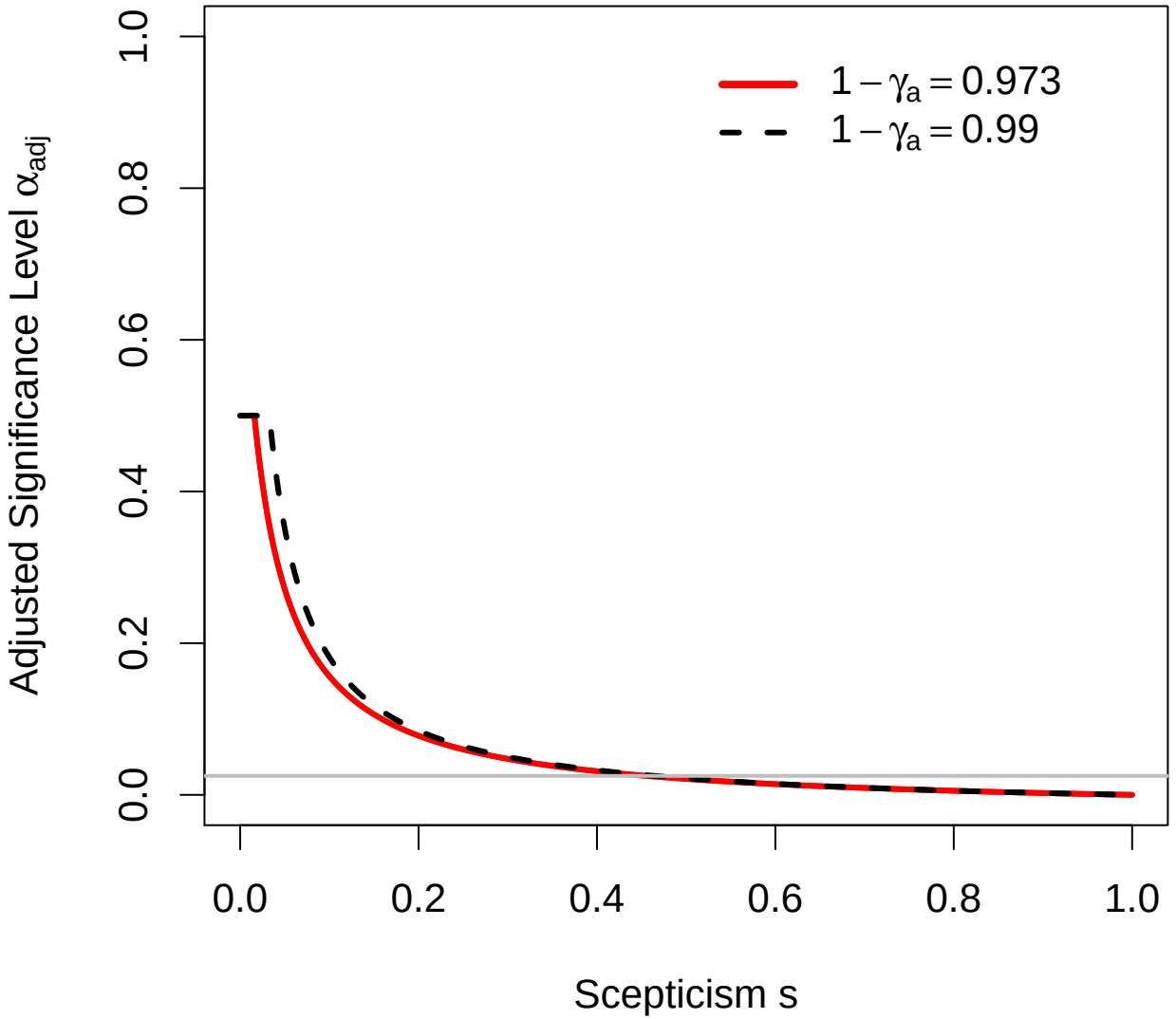

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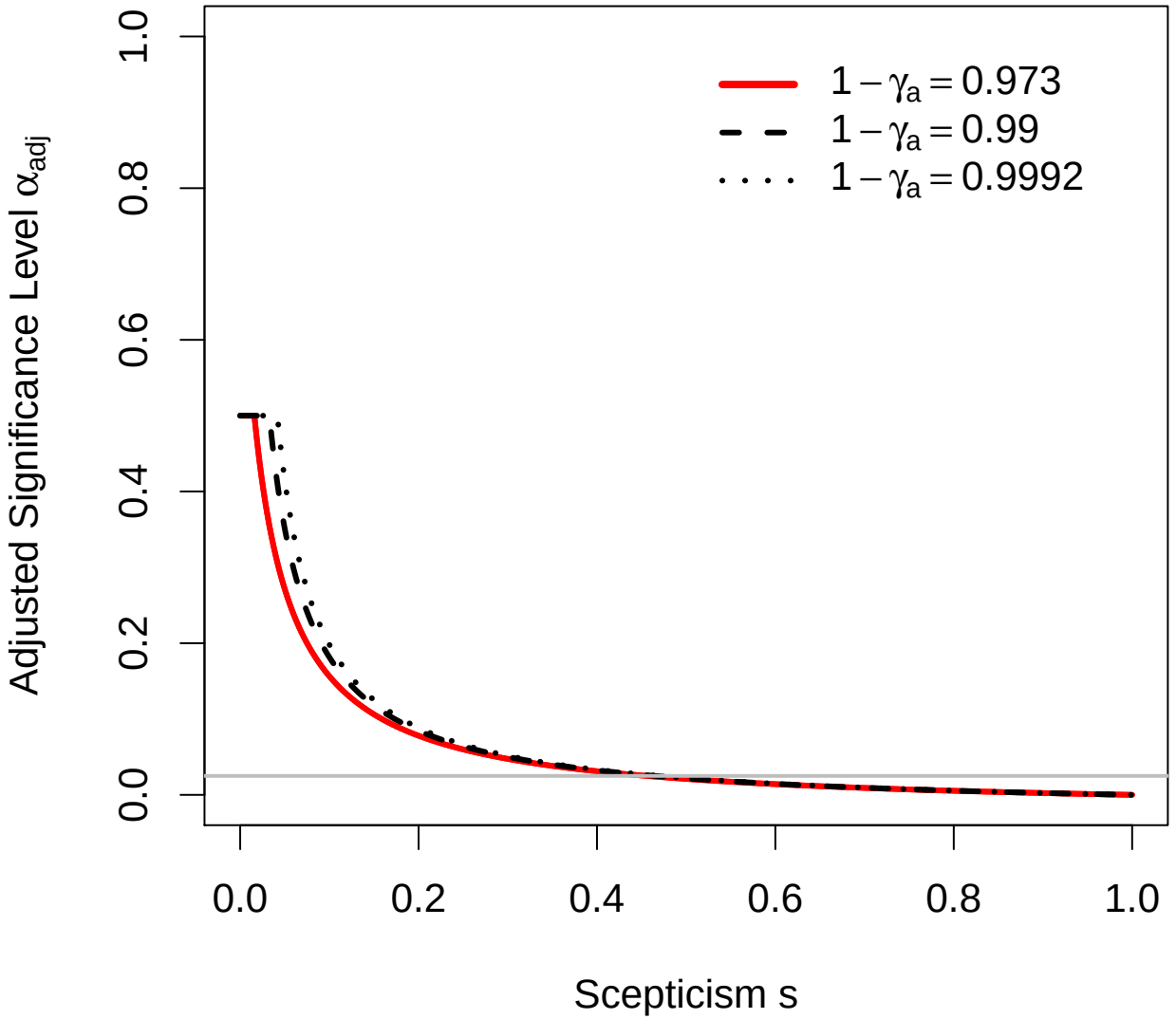

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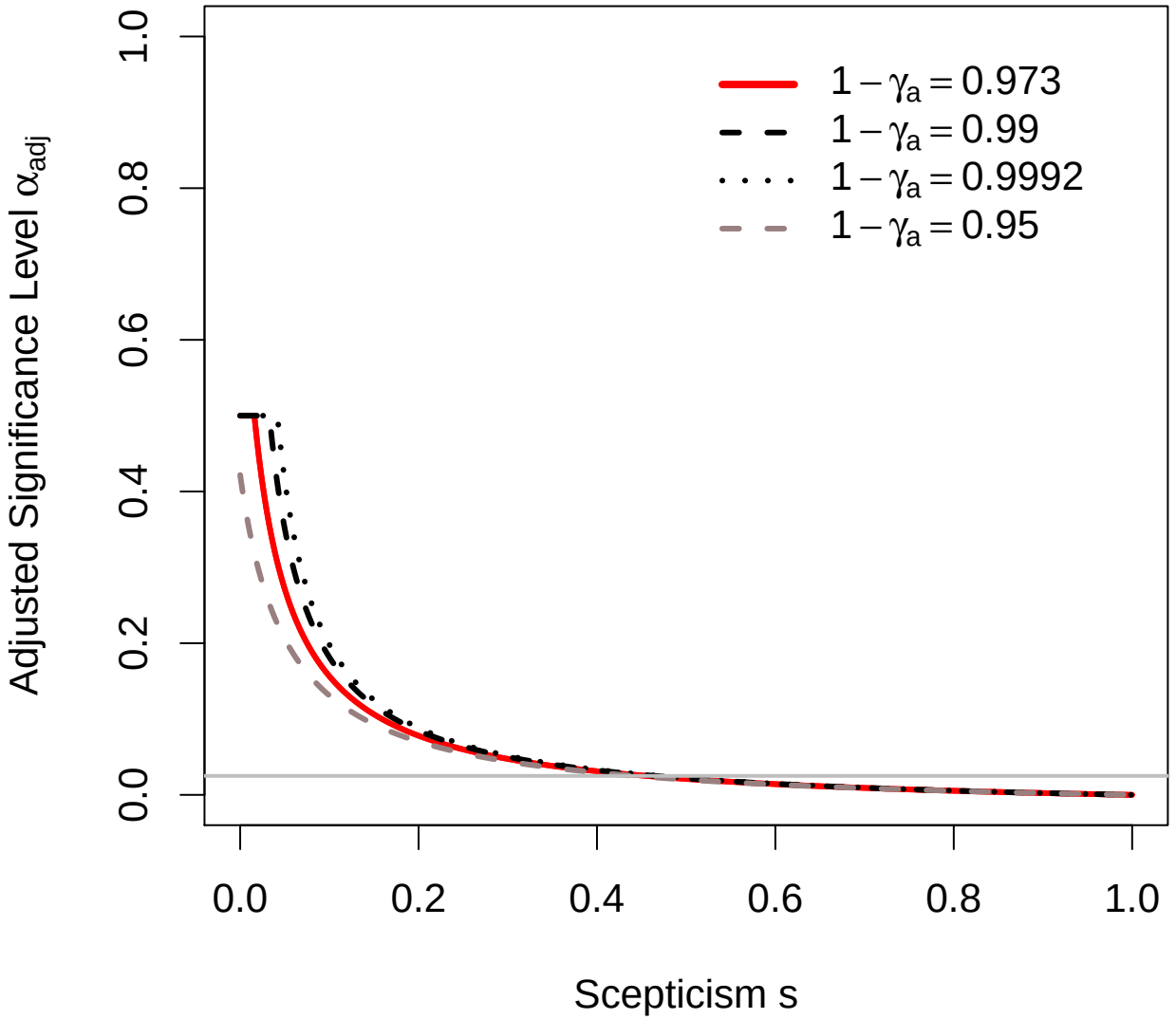

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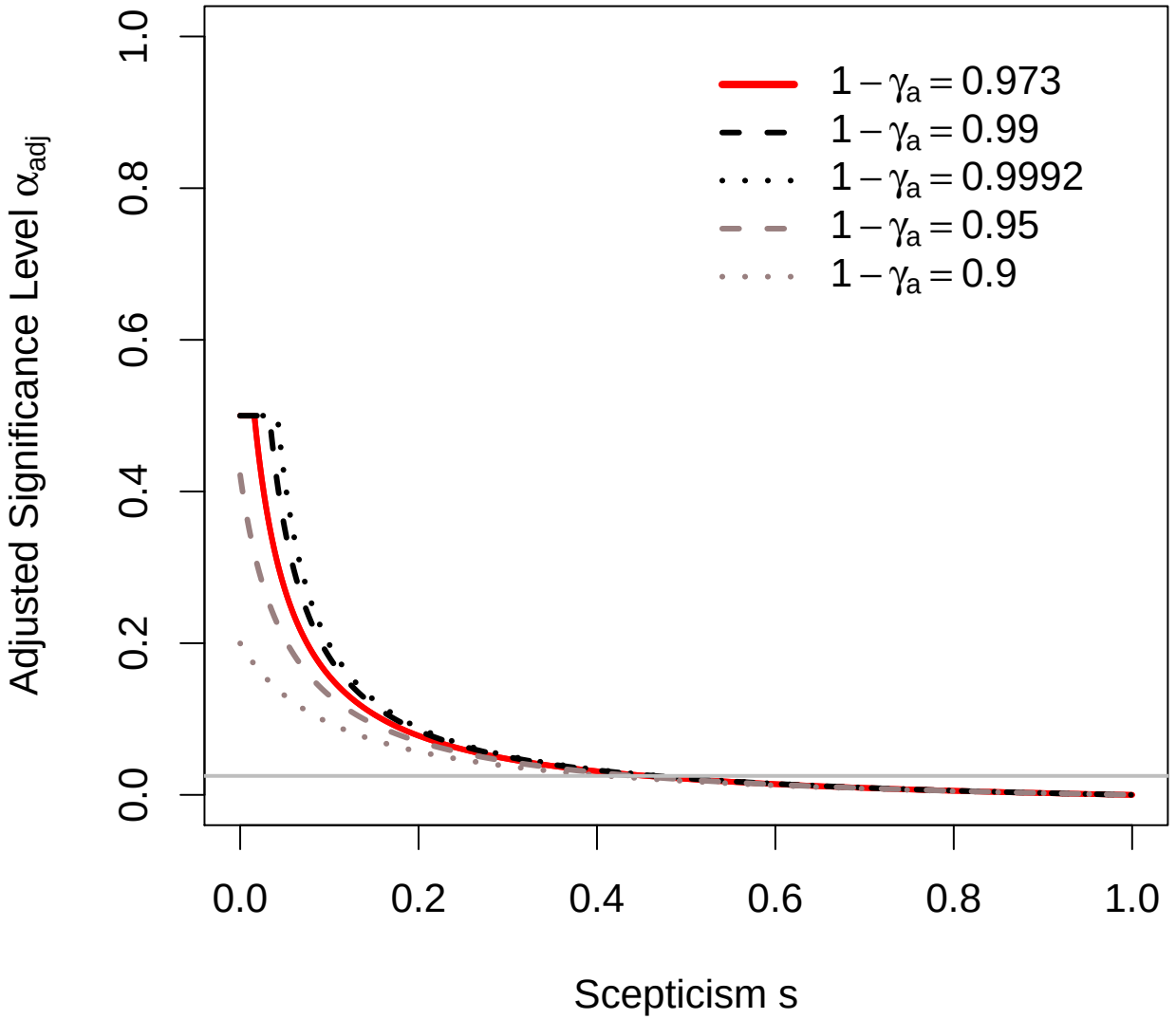

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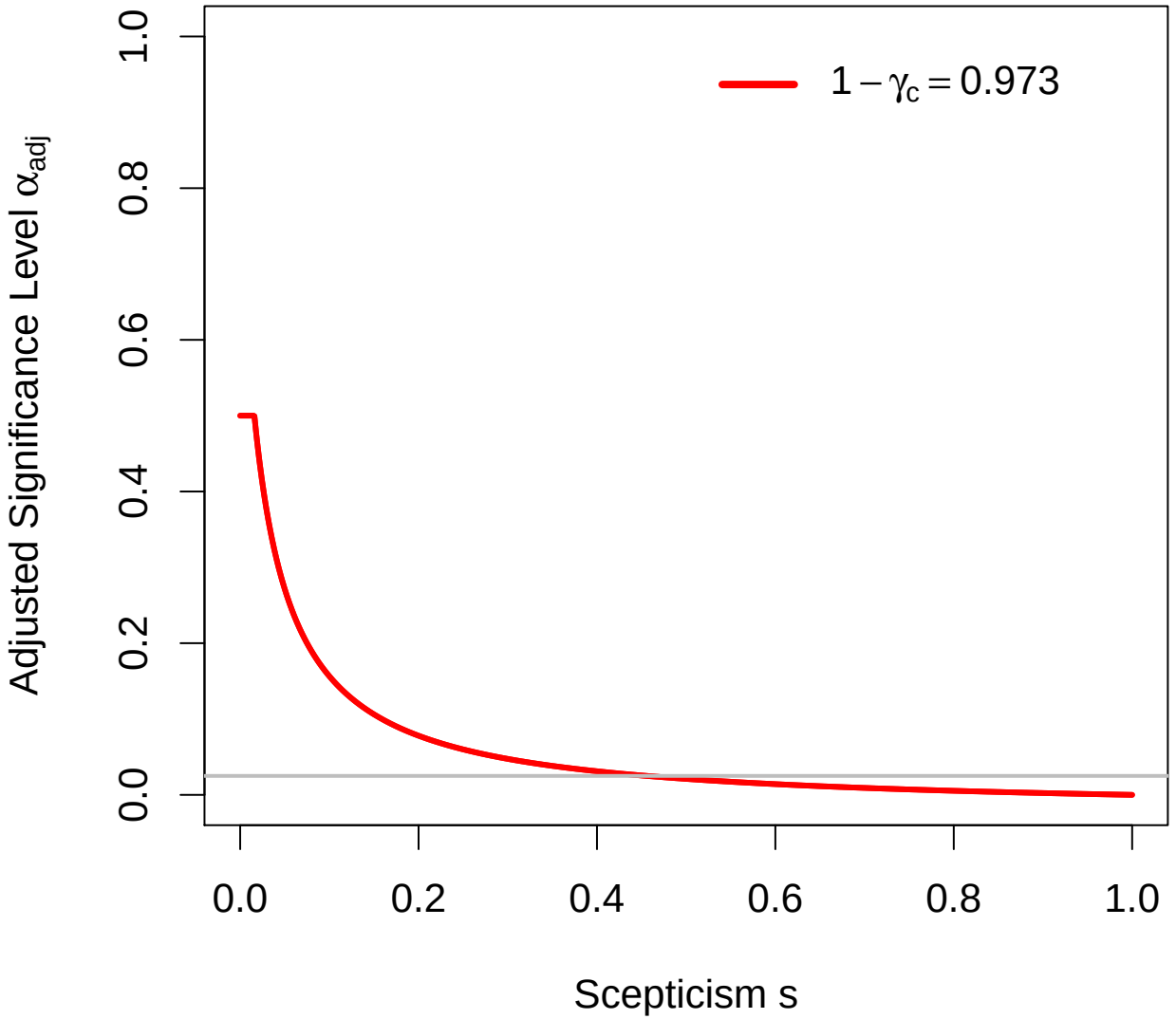

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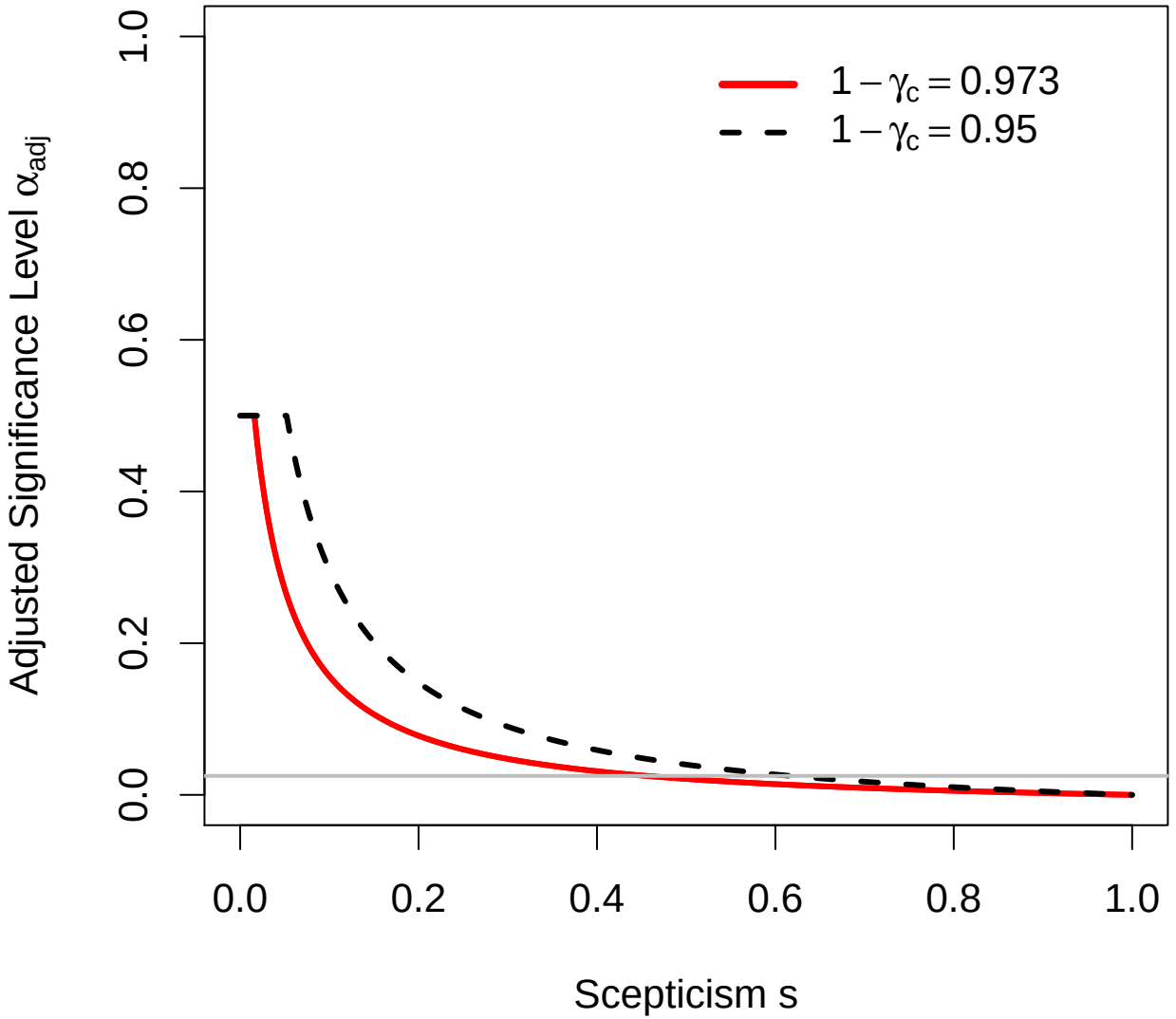

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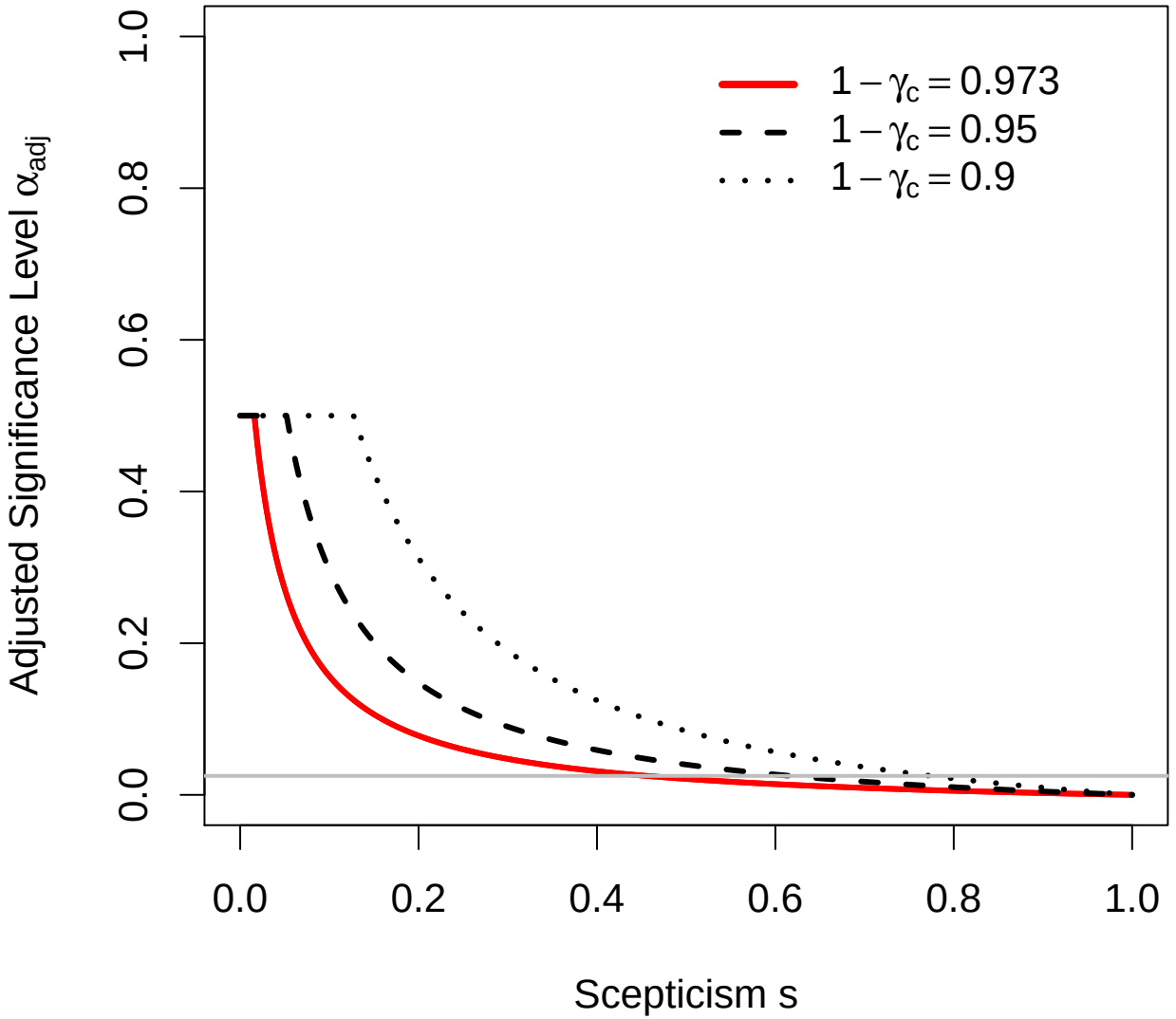

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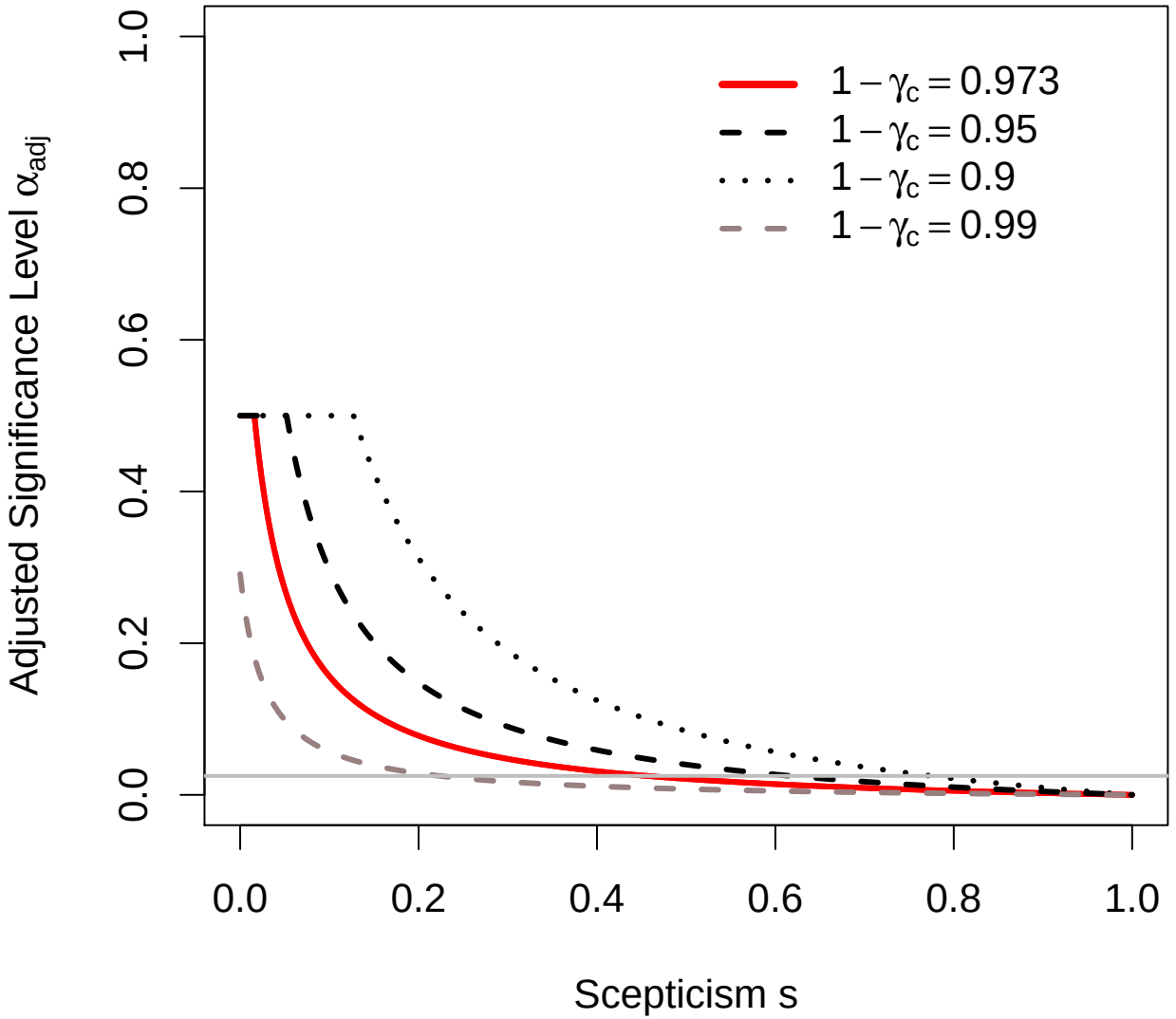

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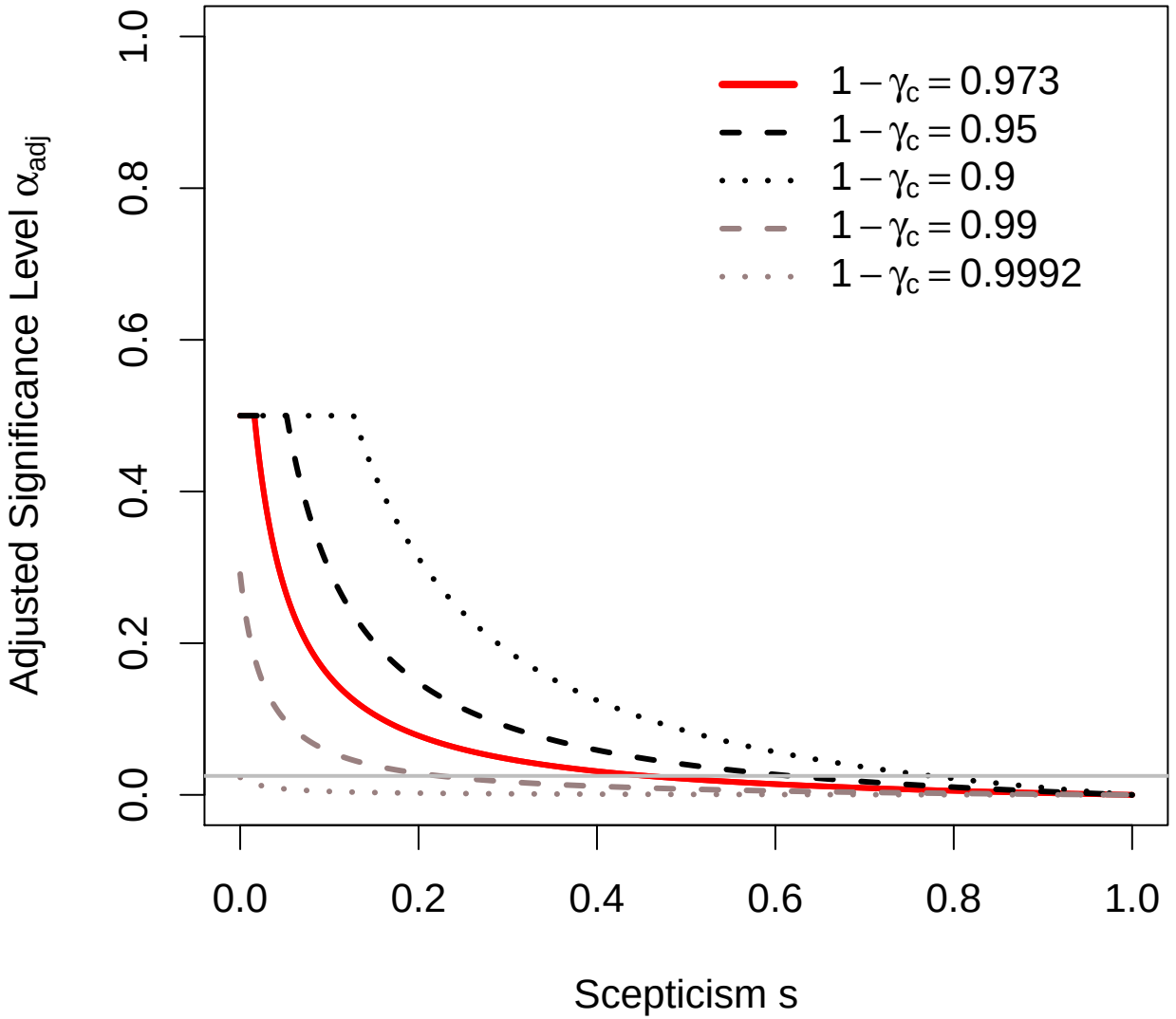

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- Assumed probability of efficacy without extrapolation $1-q = 0$

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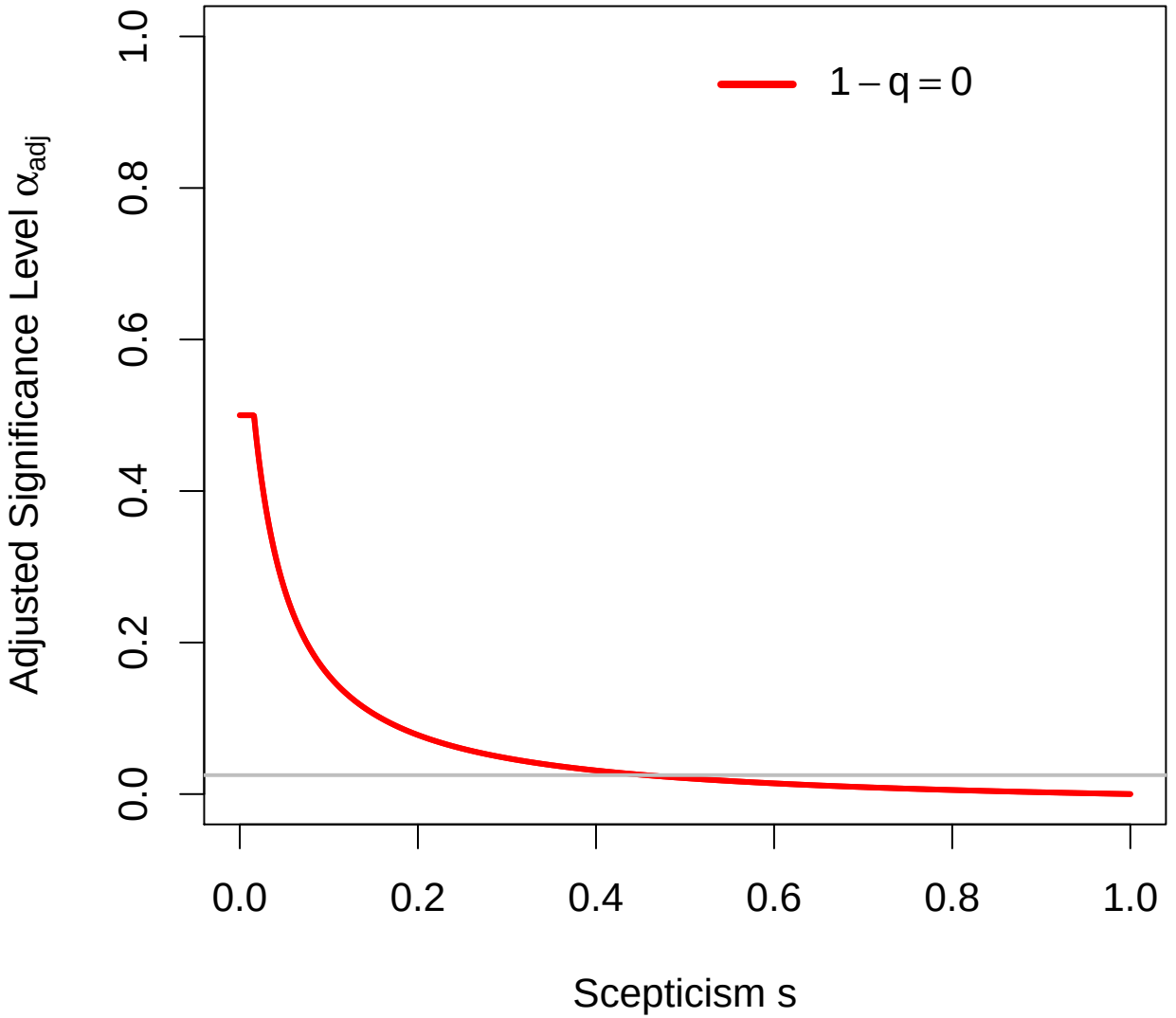

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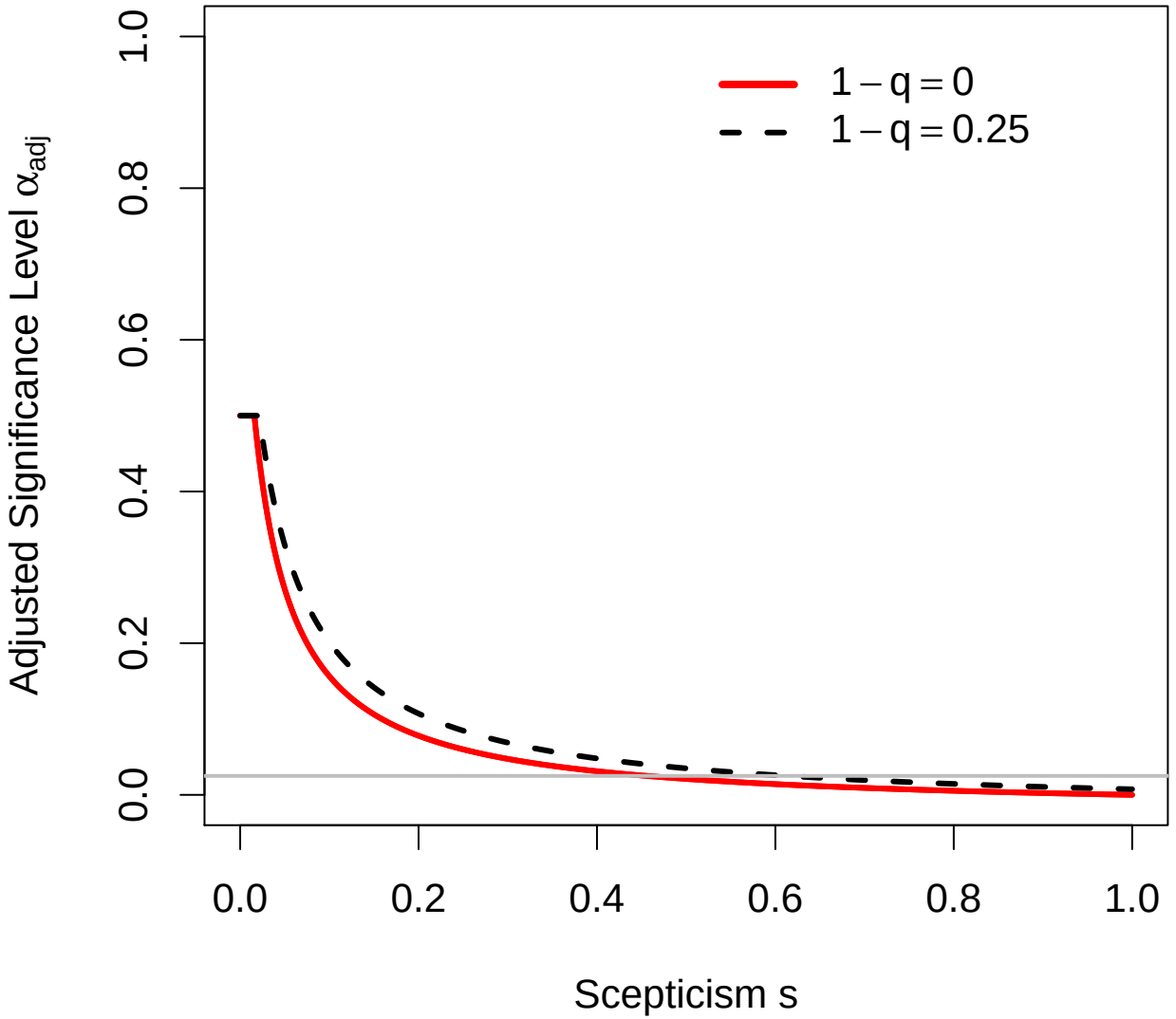

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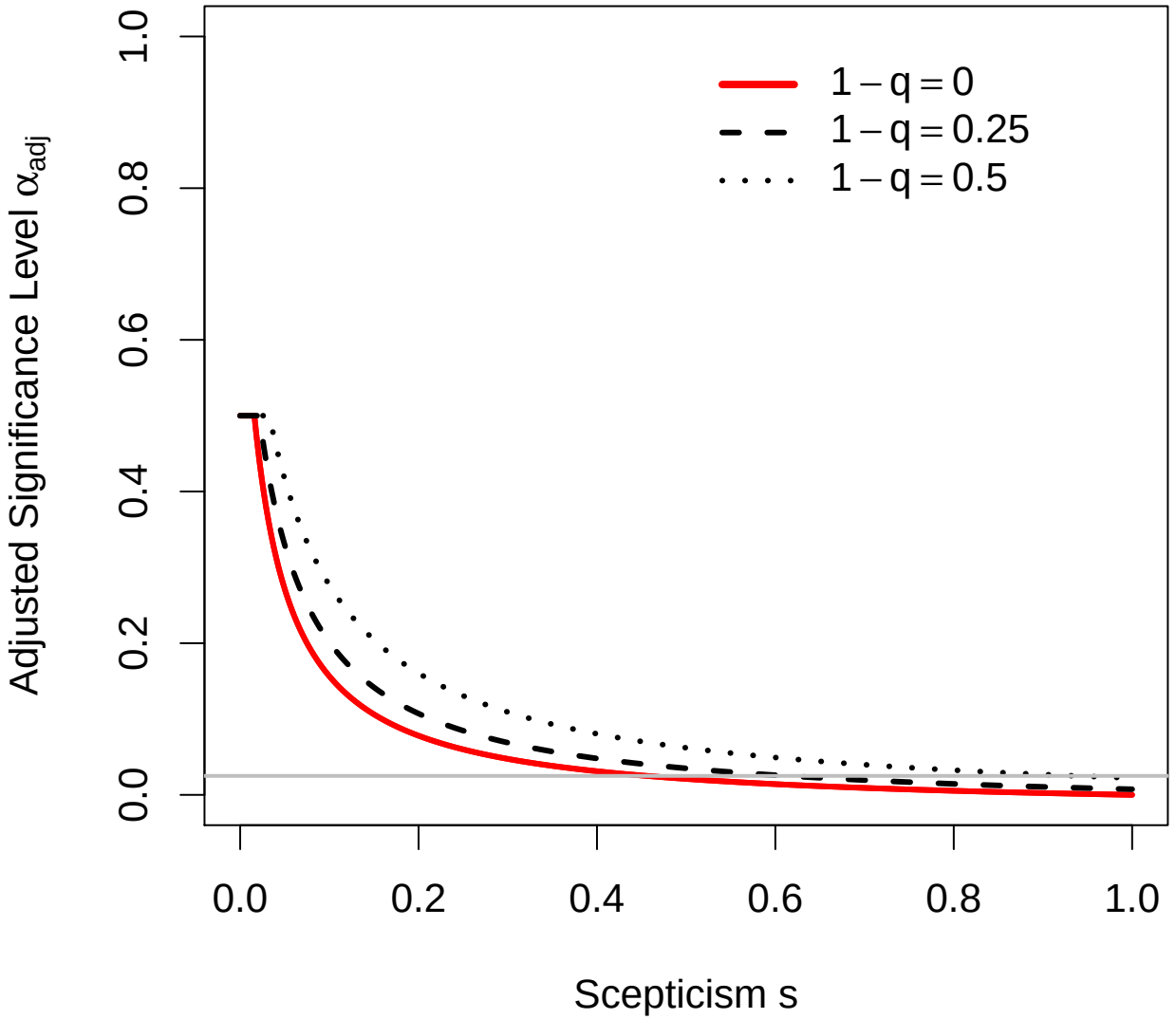

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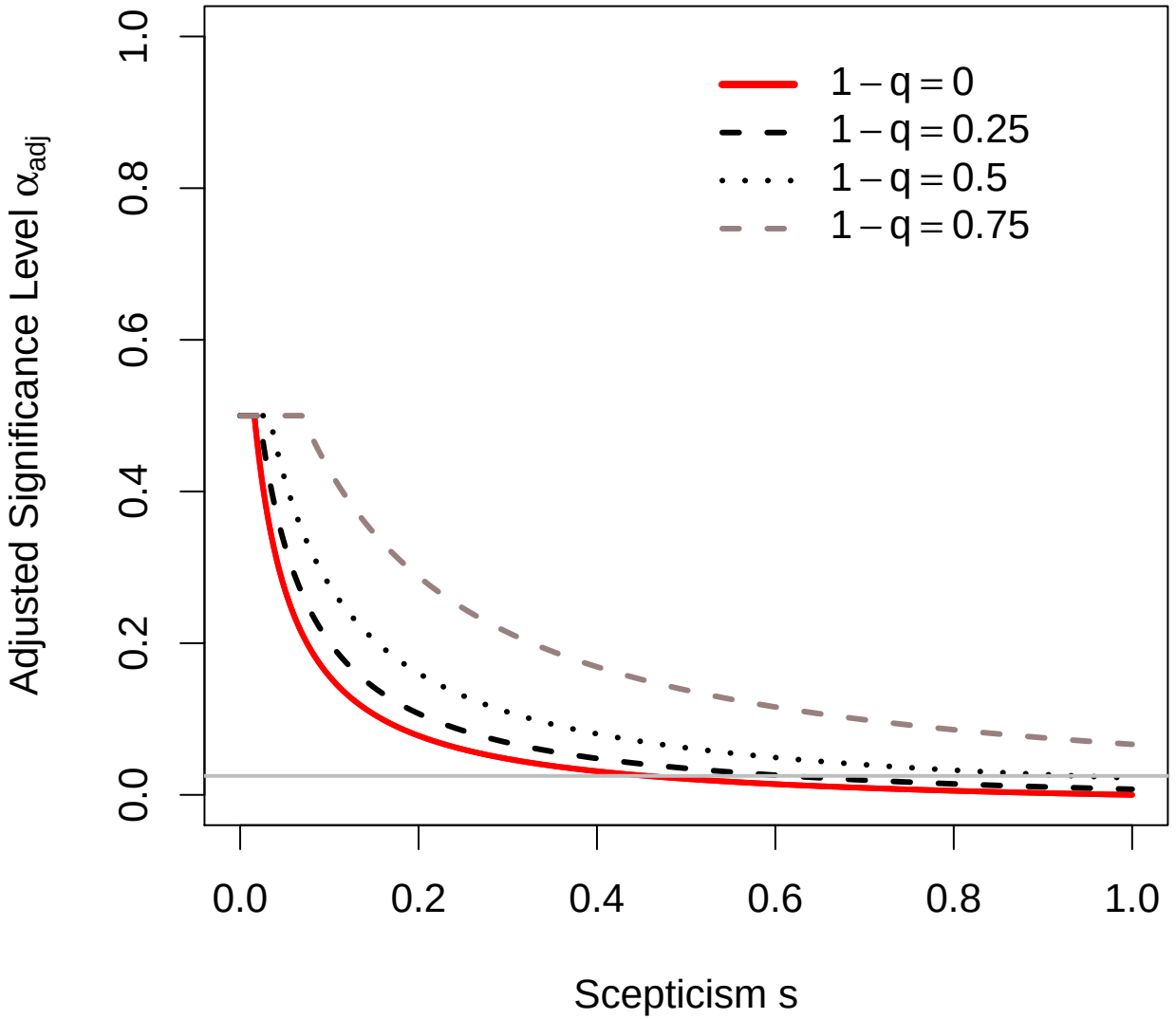

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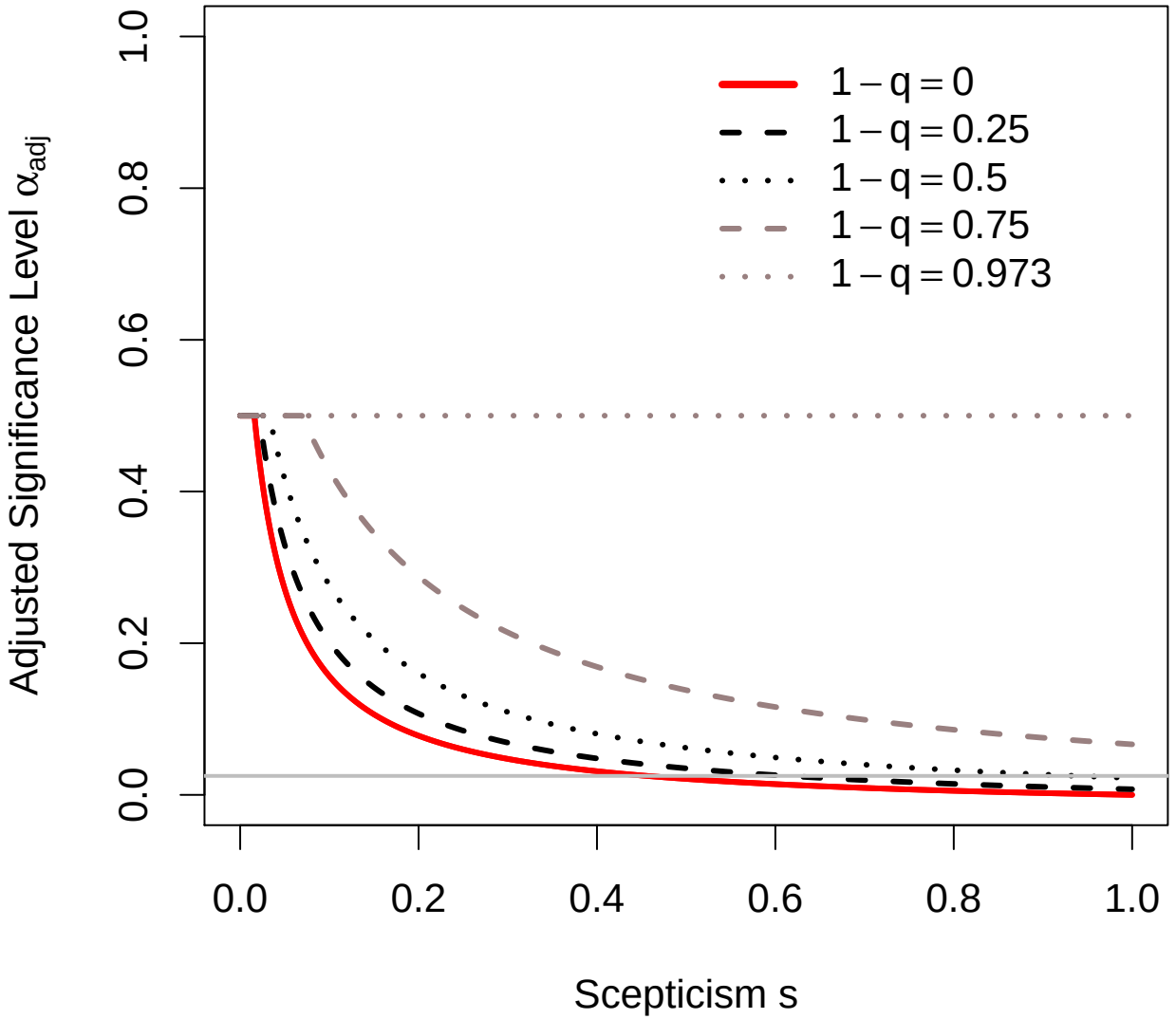

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Case Study Humira

- 2003 registration of Adalimumab at the EMA for moderate and severe active rheumatoid arthritis in adult patients.
- 2008 registration for juvenile ideopathic arthritis based on a single randomized withdrawal study in paediatric patients:
  - Primary outcome measure: proportion of patients who had a disease flare during the 32 week double-blind phase
  - Significance level: 0.05 (two-sided). Power: 0.8 for a 40 % difference between treatments.
  - In the population of primary interest a p-value of $p = 0.03$ for the primary outcome measure has been observed.
- The committees concerned agree that a single successful confirmatory study would be sufficient for registration.

Which scepticism s is compatible with this strategy in our framework?

Case Study (continued)

What is the maximum Scepticism factor such that only one instead of two pivotal studies at level 0.025 (one-sided) are required to achieve the same final confidence in efficacy as in adults?

$1 - q = 0, 1 - \beta_a = 1 - \beta_c = 0.80$

Prior Adults $1 - r_a$	0.1	0.3	0.5	0.7	0.9
Posterior Adults $1 - \gamma_a$	.9930	.9982	.9992	.9997	.9999
Maximal Scepticism s $(1 - \gamma_c = 1 - \gamma_a)$	.178	.053	.024	.010	.003
Maximal Scepticism s $(1 - \gamma_c = 0.9992)$	.018	.023	.024	0.025	0.025
Maximal Scepticism s $(1 - \gamma_c = 0.973)$	.467	.469	.470	.470	.470

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Required Input from Experts

Fixing of

- the Scepticism factor s.
- the success rate of new compounds in a special class of diseases and compounds or, alternatively the targeted confidence in efficacy in adults $1 - \gamma_a$ given a successful adult development.
- the prior confidence in efficacy in children if extrapolation is not possible $(1 - q)$

How to quantify Scepticism? A challenge to the Experts.

- In an early stage, when a PIP has to be assessed, often no Phase III data from adult studies are available (as PIPs should be provided as early as possible).
- Therefore, the quantification has to rely on expert opinion concerning the disease, the patient population, the medicinal product, ...
- Specific methods for elicitating prior beliefs in Bayesian statistics may be applied also here.
- Modeling and simulation may give guidance on the translation of treatment effects from adults to children. The scepticism s can then quantify the uncertainty of the models.

What confidence in efficacy is required in drug regulation?

- Is it reasonable to require confidence levels of 0.9992 (0.973) for drug licensing?
- Is it reasonable to require lower confidence levels in vulnerable populations?
- A fully decision theoretic approach would require to specify overall utility functions accounting for false positive and false negative conclusions, benefits and risks. This would give guidance on the level of confidence $(1 - \gamma_c)$ in efficacy that should be required for children?

Application in the Regulatory Context

- The environment of extrapolation is likely to change after a PIP has been agreed on in an early phase, when later data from adult studies will become available.
- Requests for modification of an approved PIP is an appropriate way to account for the data in adults. However, currently only the company can ask for a modification.
- If these data become available, other Bayesian approaches may be applied to adaptively modify the pre-planned paediatric development programme.
- The framework formally incorporates prior information and expert knowledge, while still applying frequentist testing albeit at a modified significance level.

Backup Slides

Discrete versus Two Point Priors

- The framework is based on two point priors
  - H_0^a ... drug is not efficacious in adults ($\Delta = 0$)
  - H_1^a ... drug is efficacious with a treatment effect $\Delta = \Delta_1 > 0$.
- However, a generalization to continuous priors is possible.

How robust is the determination of $1 - r_a$?

Historic Success Rate	α_{historic}	$1 - \beta_{\text{historic}}$	$1 - r_a$
0.4	0.025	0.9	0.43
		0.8	0.48
		0.7	0.56
	0.025^2	0.9	0.44
		0.8	0.50
		0.7	0.57
0.3	0.025	0.8	0.35
	0.025^2	0.8	0.37

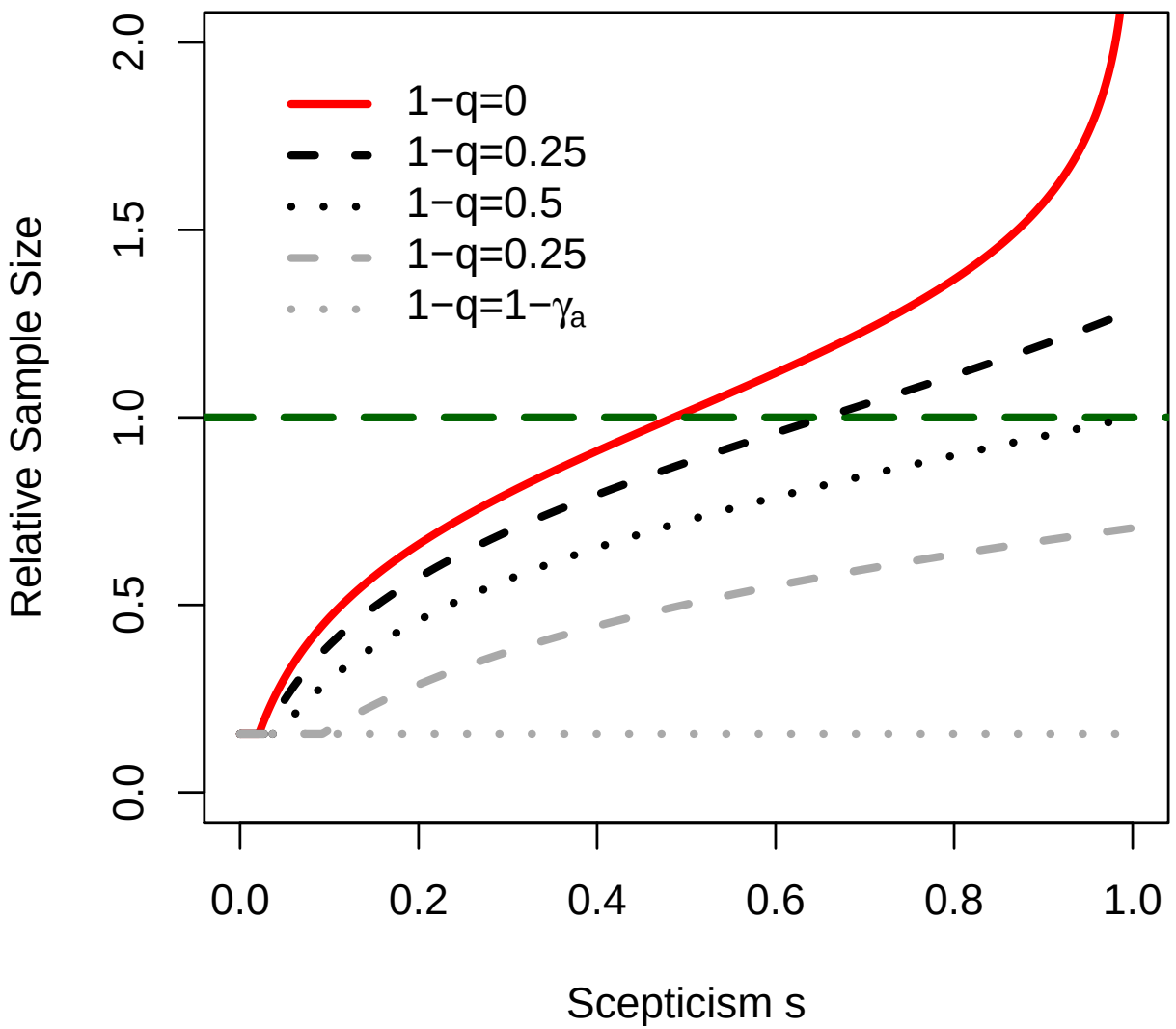
Computation of $1 - r_a$

$1 - r_a$ solves: Historic Success Rate $= (1 - \beta_{\text{historic}})(1 - r_a) + \alpha_{\text{historic}} r_a$.

How sensitive does $1 - \gamma_a$ depend on the assumptions?

Prior Adults $1 - r_a$	Significance Level α_a	Power $1 - \beta_a$	Posterior Adults $1 - \gamma_a$
0.5	0.025	0.9	0.9730
		0.8	0.9697
		0.7	0.9655
	0.025^2	0.9	0.9993
		0.8	0.9992
		0.7	0.9991
0.3	0.025	0.8	0.9320
	0.025^2	0.8	0.9982

Sample Size Reduction



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