Objective Bayesian Inference for Bilateral Data

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Abstract. This paper presents three objective Bayesian methods for analyzing bilateral data under Dallal's model and the saturated model. Three parameters are of interest, namely, the risk difference, the risk ratio, and the odds ratio. We derive Jeffreys' prior and Bernardo's reference prior associated with the three parameters that characterize Dallal's model. We derive the functional forms of the posterior distributions of the risk difference and the risk ratio and discuss how to sample from their posterior distributions. We demonstrate the use of the proposed methodology with two real data examples. We also investigate small, moderate, and large sample properties of the proposed methodology and the frequentist counterpart via simulations.

Keywords: Bayes factor, Dallal's model, Jeffreys' prior, Odds ratio, Product trinomial distribution, Reference prior, Risk difference, Risk ratio.

1 Introduction

Bilateral data arise in medicine when a group of randomly chosen patients with a condition receive a new treatment, for example, surgery, on paired body parts within the same individual (eyes, ears, breasts, arms, hands, knees, legs, or feet), while another group of patients with this condition receive a control treatment, for example, the currently accepted medical treatment. The investigator records paired Bernoulli outcomes about a particular characteristic, for example, absence of the condition, that are then grouped into one of three categories. (i) The two body parts are cured, recorded as $(1, 1)$. The counts of patients with this characteristic from the control and treatment groups are denoted by m_{20} and m_{21}. (ii) One of the two body parts is cured while the other remains diseased, recorded as $(1, 0)$ or $(0, 1)$. However, these $(1, 0)$ and $(0, 1)$ outcomes are thrown away and this detailed information is no longer available. Only the counts of patients from the control and treatment groups in that category, m_{10} and m_{11} are available. (iii) Neither of the two body parts are cured, denoted by $(0, 0)$. The counts of patients in this category from the control and treatment groups are denoted by m_{00} and m_{01}. The data, denoted by D, can be summarized into a 3×2 contingency table (see Table 1) where the trinomial counts (m_{01}, m_{11}, m_{21}) for the treatment group and (m_{00}, m_{10}, m_{20}) for the control group are the cell entries. Such data are very common in ophthalmologic, orthopaedic and otolaryngologic studies. Twin studies are also a familiar source of bilateral data. The goal of such clinical trials is to quantify the benefit of treatment over placebo.

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Table 1: Data structure for bilateral data along with their corresponding trinomial probabilities. $p_{00} + p_{10} + p_{20} = 1 = p_{01} + p_{11} + p_{21}$, $m_{00} + m_{10} + m_{20} = m_{+0}$ and $m_{01} + m_{11} + m_{21} = m_{+1}$ are fixed by design.

Numbers of cured organs	Group	
	Treatment	Control
0	$m_{01}\ (p_{01})$	$m_{00}\ (p_{00})$
1	$m_{11}\ (p_{11})$	$m_{10}\ (p_{10})$
2	$m_{21}\ (p_{21})$	$m_{20}\ (p_{20})$
Total	m_{+1}	m_{+0}

The main parameter in bilateral models is the difference between the proportion of body parts (λ_0, λ_1) with the characteristic of interest in the two groups, $\Delta = \lambda_1 - \lambda_0$. However, the dependency between paired observations cannot be ignored. Rosner (1982), Morris (1993), and Tang et al. (2006) discuss the consequences of ignoring this dependency.

Five models have been proposed for bilateral data: Rosner's model, Dallal's model, the equal correlation model, the independence model, and the full or saturated model. Of these five models, the most extensively studied is Rosner's model. Tang et al. (2008) present several test statistics for the equality of λ_0 and λ_1 under Rosner's model. Qiu et al. (2009) consider the problem of sample size calculations under Rosner's model. Tang et al. (2011) discuss various techniques to construct asymptotic confidence intervals for Δ under Rosner's model and evaluate the performance of these via empirical studies. Tang et al. (2010) is perhaps the only paper that discusses all five models simultaneously to determine which one provides a better fit to the data. Pei et al. (2010) present asymptotic confidence intervals under the equal correlation model and evaluate their performance. Pei et al. (2008) present a test for the equality of λ_0 and λ_1 when unilateral and bilateral data are combined under the equal correlation model.

Among these five models, the independence model is rarely used in practice in the context of bilateral data. The objective priors for the saturated model have already been investigated in the literature. The challenge with Rosner's model is that it is difficult to justify this model from a biological point of view. Only the equal correlation model and the equal conditional probability model (Dallal's model) have sound statistical foundations and biological interpretation. Indeed, one can always characterize a bivariate discrete distribution for two binary random variables by making assumptions about (i) their marginal distributions and the correlation they share or (ii) their marginal distributions and the two conditional distributions they share. For Rosner's model and the equal correlation model, Jeffreys' prior and Bernardo's reference prior are too complex to be of much practical use. Dallal's model is the only model for which we could derive useful closed-form expressions for various objective priors. For these reasons, we solely focus on Dallal's model in this paper.

Bayesian methods have gained incredible popularity in recent years both in the theory and practice of statistics. Under non-informative priors, Bayesian inferences yield results similar to that obtained under the frequentist paradigm. As we will show in an example presented in Section 5.2, Bayesian inference for Dallal's model yields similar findings to the corresponding frequentist analysis. Bayesian methods, however, do not rely on the normal approximation to carry out statistical inferences, which is an advantage over the frequentist methods. It is not unusual to encounter 3×2 bilateral data where one or more cells have sparse data, thereby preventing the use of the usual normal approximation that underlies frequentist inferences developed in Appendix 1 of the Supplementary Web Materials. Also, in some sparse 3×2 bilateral data, frequentist estimates lie on the boundary of the parameter space, which are not permitted by design. In such situations, one cannot compute the confidence intervals for some parameters or carry out tests of hypotheses about some of the parameters. We provide one such example in Section 5.1. Bayesian methods provide a simpler way to analyze such sparse bilateral data. Another benefit of Bayesian inference for 3×2 bilateral data is its ability to handle the nuisance parameter in Dallal's model which complicates frequentist analyses.

There are no existing Bayesian methods for bilateral data in the literature yet. We present objective Bayesian inferences for three parameters of interest: the risk difference, the risk ratio, and the odds ratio. In Section 2, we present Dallal's reduced model along with Dallal's full model. Section 3 is dedicated to the derivation of the objective Bayesian modeling of bilateral data. We focus primarily on deriving Jeffreys' prior and Bernardo's reference prior. We then discuss the Bayes factor in the context of hypothesis testing as well as a simulation scheme for the joint posterior distribution. Section 4 presents results of an empirical comparison between Bayesian methods and frequentist methods. Section 5 presents two illustrative case studies. In Section 6, we present two families of Bayesian prior distributions, including Jeffreys' or Bernardo's reference priors as special cases. Section 7 concludes this paper.

2 Dallal's Dependence Model

Dallal's model was presented for the first time as model 2 in Dallal (1988). Let "$i = 1$" and "$i = 0$" denote the treatment group and the control group, respectively. Denote by Z_{ijk} a binary variable such that $Z_{ijk} = 1$ if the kth site (kth body part) of the jth subject in the ith treatment group is free of disease at the end of the study and 0 otherwise for $i = 0, 1$, $j = 1, \ldots, m_{+i}$, and $k = 1, 2$. Dallal's (reduced) model is characterized by the following assumptions:

Assumption 1: $P\big(Z_{ijk} = 1\big) = \lambda_i$ for $i = 0, 1$ with $0 < \lambda_i < 1$.

Assumption 2: $P\big(Z_{ijk} = 1 \mid Z_{ij(3-k)} = 1\big) = 1 - \gamma$ with $0 < \gamma < 1$.

Assumption 2 states that the conditional probability of an occurrence of a particular characteristic at one site given an occurrence of that characteristic at the other site to

be the same in the two treatment groups. This statement is relaxed and replaced by $P\big(Z_{ijk} = 1 \mid Z_{ij(3-k)} = 1\big) = 1 - \gamma_i$ with $0 < \gamma_i < 1$, $i = 0, 1$ in the full or saturated model. That is, two conditional probability statements are made, one for the treatment group and the other for the control group. We also refer to this saturated model as Dallal's saturated model. However, the full model has one more parameter than the reduced model.

Let m_{hi} be the number of subjects in the ith group with exactly h site(s) cured and p_{hi} be the success probability associated with m_{hi} for $h = 0, 1, 2$ and $i = 0, 1$. The two group total sample sizes are denoted by m_{+1} for the treatment group and m_{+0} for the control group and these are assumed fixed by design. Hence, (m_{0i}, m_{1i}, m_{2i}) follows the trinomial distribution with total number of trials m_{+i} and probability parameter vector (p_{0i}, p_{1i}, p_{2i}) for $i = 0, 1$ such as

$$p_{0i} = 1 - (1 + \gamma)\lambda_i, \ \ p_{1i} = 2\gamma\lambda_i, \ \text{ and } \ p_{2i} = (1 - \gamma)\lambda_i.$$

Dallal's model also implies that the correlation coefficients between the Z_{ijk} variables take the form:

$$\rho_i = \mathbf{Corr}\big(Z_{ijk}, Z_{ij(3-k)}\big) = 1 - \frac{\gamma}{1 - \lambda_i}, \qquad i = 0, 1. \tag{1}$$

In fact, the conditional probability assumption in Dallal's model can be replaced by the statement in (1) about the correlation coefficient. The correlation coefficient, ρ_i, takes both positive and negative values over the entire range $(-1, 1)$. The excess risk is defined as

$$\delta_i = P(Z_{ijk} = 1 \mid Z_{ij(3-k)} = 1) - P(Z_{ijk} = 1) = 1 - \gamma - \lambda_i$$

for $i = 0, 1$.

The main parameter of interest in this investigation is the risk difference, $\Delta = \lambda_1 - \lambda_0$, and, therefore, γ can be viewed as a nuisance parameter. The risk ratio, $R = \dfrac{\lambda_1}{\lambda_0}$ and the odds ratio, $\psi = \dfrac{\lambda_1(1 - \lambda_0)}{(1 - \lambda_1)\lambda_0}$ can also be of interest. Another parameter of interest is the difference of excess risks in both the treatment and the control groups, $\delta_0 - \delta_1$, which is equal to Δ under Dallal's reduced model. To date, the risk ratio, the odds ratio and the difference of excess risks have never been discussed in the bilateral data literature. The first two parameters add another dimension to the utility of bilateral data so that they can be collected under either a prospective study paradigm or a retrospective observational study paradigm, allowing for more applications than those under the current clinical setting. Although the addition of these new parameters poses more challenges for carrying out frequentist inference, no additional work is required in the Bayesian framework.

What makes the inferential process challenging in Dallal's model is that one deals with a constrained parameter space. Indeed, the parameter space is

$$\Omega = \left\{ (\gamma, \lambda_0, \lambda_1) : \quad 0 < \gamma < 1 \text{ if } 0 < \max(\lambda_0, \lambda_1) \le \frac{1}{2}; \right.$$
$$\left. 0 < \gamma < \frac{1}{\max(\lambda_0, \lambda_1)} - 1 \text{ if } \max(\lambda_0, \lambda_1) > \frac{1}{2} \right\}$$

or equivalently

$$\Omega = \left\{ (\gamma, \lambda_0, \lambda_1) : \quad 0 < \gamma < 1 \text{ and } 0 < \lambda_0, \lambda_1 < \frac{1}{1 + \gamma} \right\}. \tag{2}$$

We adopt the second representation in the sequel.

The likelihood function can be expressed as

$$
\begin{aligned}
L(\gamma, \lambda_0, \lambda_1) &= \prod_{i=0}^{1} \binom{m_{+i}}{m_{0i}, m_{1i}, m_{2i}} \left[1 - (1 + \gamma)\lambda_i \right]^{m_{0i}} (2\gamma\lambda_i)^{m_{1i}} \left[(1 - \gamma)\lambda_i \right]^{m_{2i}} \\
&\propto \gamma^{m_{10}+m_{11}} (1 - \gamma)^{m_{20}+m_{21}} \lambda_0^{m_{10}+m_{20}} \lambda_1^{m_{11}+m_{21}} \left[1 - (1 + \gamma)\lambda_0 \right]^{m_{00}} \\
&\quad \times \left[1 - (1 + \gamma)\lambda_1 \right]^{m_{01}}, \qquad\qquad (\gamma, \lambda_0, \lambda_1) \in \Omega.
\end{aligned}
$$

In Appendix 1 of the Supplementary Web Appendix, we develop for the first time large-sample frequentist inferences for the risk difference, the risk ratio and the odds ratio under Dallal's model.

3   Bayesian Analysis

A key component in Bayesian analysis is the choice of the prior distribution. Traditionally, Bayesians have turned to conjugate priors. However, the concept of conjugate priors is only universal in standard univariate problems. In addition, when little or no prior information is available, conjugate priors become subjective. Thus, non-informative or objective priors are more widely accepted. The uniform distribution over the parameter space is an obvious non-informative prior. Jeffreys' prior and Bernardo's reference prior are alternative choices that are invariant under any parameterization or a larger class of parameterizations. Another alternative choice is to use a joint prior that is the compromise between an informative prior and a non-informative prior (Sun and Berger, 1998).

We discuss four types of priors: the uniform prior, Jeffreys' prior, Bernardo's prior, and Sun and Berger's reference prior in light of partial information. We derive the posterior distributions of Δ and R as well as $P(\Delta > \Delta_0 \,|\, D)$ and $P(R > R_0 \,|\, D)$ in Appendix 4. Although we do not provide the posterior distribution of ψ (more complex), we discuss in Section 3.4 how to sample from the posterior distributions of Δ, R and ψ. We use the parameter values generated to compute posterior probabilities such as $P(\Delta > \Delta_0 \,|\, D), P(R > R_0 \,|\, D), P(\psi > \psi_0 \,|\, D)$, and Bayesian credible intervals. The

Bayes factors are introduced in Section 3.5 to compare the models under the hypotheses (i) H_0: $\lambda_0 = \lambda_1$ and H_1: $\lambda_1 \neq \lambda_0$ and (ii) H_0^*: $\gamma_1 = \gamma_0$ versus H_1^*: $\gamma_1 \neq \gamma_0$.

3.1   The Uniform Prior Distribution

The prior $\pi_U(\gamma, \lambda_0, \lambda_1) = 2$ for $(\gamma, \lambda_0, \lambda_1) \in \Omega$ refers to the uniform distribution under Dallal's model. This prior is proper and expresses a complete indifference of one vector of parameter values over another. The resulting posterior distribution is

$$\pi_U(\gamma, \lambda_0, \lambda_1 | D) \quad \propto \quad 2^{m_{1+}} \gamma^{m_{1+}} (1-\gamma)^{m_{2+}} \lambda_0^{m_{10}+m_{20}} \left[1 - (1+\gamma)\lambda_0\right]^{m_{00}} \lambda_1^{m_{11}+m_{21}}$$
$$\times \left[1 - (1+\gamma)\lambda_1\right]^{m_{01}}, \qquad (\gamma, \lambda_0, \lambda_1) \in \Omega, \qquad (3)$$

where $m_{1+} = m_{10} + m_{11}$ and $m_{2+} = m_{20} + m_{21}$. As a result, the marginal posterior distribution of the nuisance parameter γ is

$$\pi_U(\gamma | D) = \frac{2^{m_{1+}+1}}{\mathbf{B}(m_{1+}+1, m_{2+}+1)} \frac{\gamma^{m_{1+}}(1-\gamma)^{m_{2+}}}{(1+\gamma)^{m_{1+}+m_{2+}+2}}, \qquad 0 < \gamma < 1, \qquad (4)$$

and the conditional posterior distribution of λ_i, $i = 0, 1$ given γ is

$$\pi_U(\lambda_i | \gamma, D) \quad = \quad (1+\gamma)^{m_{1i}+m_{2i}+1} \frac{\lambda_i^{m_{1i}+m_{2i}} \left[1 - (1+\gamma)\lambda_i\right]^{m_{0i}}}{\mathbf{B}(m_{1i}+m_{2i}+1, m_{0i}+1)}, \quad 0 < \lambda_i < \frac{1}{1+\gamma}, \quad (5)$$

where $\mathbf{B}(.,.)$ refers to the Beta function. In other words, $\dfrac{1-\gamma}{1+\gamma} \sim \mathbf{Be}(m_{2+}+1, m_{1+}+1)$ and $(1+\gamma)\lambda_i | \gamma \sim \mathbf{Be}(m_{1i}+m_{2i}+1, m_{0i}+1)$, $i = 0, 1$, where the notation $\mathbf{Be}(\alpha, \beta)$ represents the standard Beta distribution with shape parameters α and β. The uniform prior can be viewed as a process of adding $1/2$ to the summary statistics in the bottom four cells of the 3×2 table and 1 to the top two cells. The uniform prior is appealing in situations where the physical system imposes a natural parameterization with a nice physical interpretation. In general, the uniform distribution lacks the property of parameterization invariance.

3.2   Jeffreys' Prior

Jeffreys' prior has the property of being invariant under a one-to-one reparameterization (Jeffreys, 1946). Regardless of the parameterization used, Jeffreys' prior distribution is proportional to the square root of the absolute value of the determinant of the Fisher's information matrix.

Define $U = (1+\gamma)\lambda_0$ or equivalently $\lambda_0 = \dfrac{U}{1+\gamma}$, and let $V = (1+\gamma)\lambda_1$ or equivalently $\lambda_1 = \dfrac{V}{1+\gamma}$. Under this new parametrization, the parameter space reduces to the interval $(0, 1)$ for each of the three parameters γ, U and V. Thus, we are no longer dealing with a constrained parameter space. Moreover, the triplet (γ, U, V) forms a set

of orthogonal parameters in the sense of Cox and Reid (1987), that is, the off-diagonal elements of the expected Fisher information matrix are all zero. Propositions 3.1 and 3.2 give Jeffreys' priors for (γ, U, V) and $(\gamma, \lambda_0, \lambda_1)$, which are derived in Appendix 1.

Proposition 3.1. *Jeffreys' prior under the parameterization* (γ, U, V) *is*

$$\pi_J(\gamma, u, v) \propto \frac{\gamma^{1/2-1}(1-\gamma)^{1/2-1}}{(1+\gamma)}(u+rv)^{1/2}u^{1/2-1}(1-u)^{1/2-1}v^{1/2-1}(1-v)^{1/2-1} \quad (6)$$

for $0 < \gamma, u, v < 1$ *and it is proper, where* $r = \dfrac{m_{+1}}{m_{+0}}$ *is the ratio of the sample sizes in the two treatment groups.*

Under Jeffreys' prior, the nuisance parameter, γ, is independent of both U and V and its marginal prior distribution is given by

$$\pi_J(\gamma) = \frac{\sqrt{2}}{\pi} \frac{\gamma^{1/2-1}(1-\gamma)^{1/2-1}}{(1+\gamma)}, \qquad 0 < \gamma < 1. \quad (7)$$

However, Jeffreys' prior depends indirectly on the sample sizes in both groups through their ratio, r.

Proposition 3.2. *In the original space, Jeffreys' prior reduces to*

$$\pi_J(\gamma, \lambda_0, \lambda_1) \quad \propto \quad \sqrt{\frac{(1+\gamma)(\lambda_0 + r\lambda_1)}{\gamma(1-\gamma)\lambda_0\lambda_1[1-(1+\gamma)\lambda_0][1-(1+\gamma)\lambda_1]}}, \quad (8)$$
$$(\gamma, \lambda_0, \lambda_1) \in \Omega.$$

The posterior distribution resulting from the use of Jeffreys' prior is

$$\pi_J(\gamma, \lambda_0, \lambda_1 | D) \propto \frac{2^{m_{1+}+1/2}}{\mathbf{B}(m_{1+}+1/2, m_{2+}+1/2)}\gamma^{m_{1+}+1/2-1}(1-\gamma)^{m_{2+}+1/2-1}(1+\gamma)^{1/2}$$
$$\times (\lambda_0 + r\lambda_1)^{1/2}\lambda_0^{m_{10}+m_{20}+1/2-1}[1-(1+\gamma)\lambda_0]^{m_{00}+1/2-1}$$
$$\times \lambda_1^{m_{11}+m_{21}+1/2-1}[1-(1+\gamma)\lambda_1]^{m_{01}+1/2-1}, \qquad (\gamma, \lambda_0, \lambda_1) \in \Omega. \quad (9)$$

3.3 Reference Priors

Despite its success in the one-parameter context, Jeffreys' non-informative prior methodology often runs into serious difficulties in multiparameter problems (Datta and Ghosh, 1996). The prior distribution may be difficult to derive and too complex to be easily interpretable. This is often the case when several nuisance parameters are present. For our problem, Jeffreys' prior is difficult to interpret given that it depends on the ratio of sample sizes m_{+1} and m_{+0}. In this context, the reference prior may be more preferred (Bernardo, 1981; Berger and Bernardo, 1989), loosely defined as vague priors with the

least amount of information. Here, we divide the vector of parameters into two sets: parameters of interest and nuisance parameters. Then, we consider the parameters sequentially in the process of deriving a reference prior. Berger and Bernardo (1992a,b,c) took this idea to another level by suggesting to split the parameter vector into multiple groups according to their orders of inferential importance. The two authors provided a general algorithm for the construction of reference priors. Hence, reference priors are not uniquely defined. We derive the reference prior for the parameters γ, U, and V, leading to an induced reference prior for γ, λ_0, and λ_1.

We start with the two group orderings: (i) $\{U, V\}$ and then $\{\gamma\}$ and (ii) $\{V, U\}$ and then $\{\gamma\}$.

Proposition 3.3. *Bernardo's reference prior corresponding to the groups ordering $\{U, V\}$ and then $\{\gamma\}$ or $\{V, U\}$ and then $\{\gamma\}$ is*

$$\pi_R(\gamma, u, v) = \frac{2^{1/2}\gamma^{1/2-1}(1-\gamma)^{1/2-1}}{\mathbf{B}(1/2, 1/2)(1+\gamma)} \frac{u^{1/2-1}(1-u)^{1/2-1}}{\mathbf{B}(1/2, 1/2)} \frac{v^{1/2-1}(1-v)^{1/2-1}}{\mathbf{B}(1/2, 1/2)}, \qquad (10)$$

$0 < \gamma, u, v < 1$. *That is,* $\dfrac{1-\gamma}{1+\gamma} \sim \mathbf{Be}(1/2, 1/2)$, $U \sim \mathbf{Be}(1/2, 1/2)$ *and* $V \sim \mathbf{Be}(1/2, 1/2)$.

Proposition 3.4. *In the original parameterization,* $(\gamma, \lambda_0, \lambda_1)$, *Bernardo's reference prior is equivalent to*

$$\pi_R(\gamma, \lambda_0, \lambda_1) = \frac{\sqrt{2}}{\pi}\gamma^{1/2-1}(1-\gamma)^{1/2-1}\frac{\lambda_0^{1/2-1}\big[1-(1+\gamma)\lambda_0\big]^{1/2-1}}{\mathbf{B}(1/2, 1/2)}$$

$$\times \frac{\lambda_1^{1/2-1}\big[1-(1+\gamma)\lambda_1\big]^{1/2-1}}{\mathbf{B}(1/2, 1/2)}, \qquad (\gamma, \lambda_0, \lambda_1) \in \Omega. \qquad (11)$$

The proofs of Propositions 3.3 and 3.4 are given in Appendix 2.

Unlike Jeffreys' prior, γ, U, and V are independent under Bernardo's reference prior. The posterior distribution resulting from the use of Bernardo's reference prior is

$$\pi_R\big(\gamma, \lambda_0, \lambda_1|D\big)$$
$$\propto \frac{2^{m_{1+}+1/2}}{\mathbf{B}(m_{1+}+1/2, m_{2+}+1/2)}\gamma^{m_{1+}+1/2-1}(1-\gamma)^{m_{2+}+1/2-1}\lambda_0^{m_{10}+m_{20}+1/2-1}$$
$$\times \big[1-(1+\gamma)\lambda_0\big]^{m_{00}+1/2-1}\lambda_1^{m_{11}+m_{21}+1/2-1}\big[1-(1+\gamma)\lambda_1\big]^{m_{01}+1/2-1},$$

$(\gamma, \lambda_0, \lambda_1) \in \Omega$ or equivalently

$$\pi_R\big(\gamma, u, v|D\big)$$
$$= \frac{2^{m_{1+}+1/2}}{\mathbf{B}(m_{1+}+1/2, m_{2+}+1/2)}\frac{\gamma^{m_{1+}+1/2-1}(1-\gamma)^{m_{2+}+1/2-1}}{(1+\gamma)^{m_{1+}+m_{2+}+1}}$$
$$\times \frac{u^{m_{10}+m_{20}+1/2-1}(1-u)^{m_{00}+1/2-1}}{\mathbf{B}(m_{10}+m_{20}+1/2, m_{00}+1/2)}\frac{v^{m_{11}+m_{21}+1/2-1}(1-v)^{m_{01}+1/2-1}}{\mathbf{B}(m_{11}+m_{21}+1/2, m_{01}+1/2)},$$

$0 < \gamma, u, v < 1$. The reference prior can be viewed as adding $1/4$ to each of the bottom four cells of the 3×2 table and $1/2$ to the top two cells.

Ghosh and Mukerjee (1992) advise reversing the role of parameters of interest and nuisance parameters to obtain a reverse reference prior. That is, reconsider the group ordering of $\{\gamma\}$ and then $\{U, V\}$ or $\{\gamma\}$ and then $\{V, U\}$. The reference prior remains unchanged as shown in Appendix 2. We also discuss the idea of reference priors under the partial information introduced by Sun and Berger (1998) and known as conditional reference priors in Appendix 2.

3.4   Sampling from the Posterior Distribution

With analytical solutions difficult to derive or compute, we turn to Monte-Carlo simulation methods. We first discuss how to simulate γ from the distribution

$$f(\gamma) \;=\; \frac{2^{\mu}}{\mathbf{B}(\mu, \nu)} \frac{\gamma^{\mu-1}(1-\gamma)^{\nu-1}}{(1+\gamma)^{\mu+\nu}}, \qquad 0 < \gamma < 1,$$

which includes the marginal posterior distributions, $\pi_U(\gamma \,|\, D) = \pi_J(\gamma \,|\, D)$, as special cases with $\mu = m_{1+} + \frac{1}{2}$ and $\nu = m_{2+} + \frac{1}{2}$. Then, we discuss how to simulate (λ_1, λ_0) jointly from $f(\lambda_1, \lambda_0 \,|\, D)$.

We propose two direct and efficient approaches to generate γ from $f(\gamma)$.

(i) Let $\gamma = \dfrac{e^{\Psi}}{1 + e^{\Psi}}$. We show in Appendix 3 that $\phi = \Psi - \log(2)$ has the same distribution as $\mathrm{logit}(p) = \log\left(\dfrac{p}{1-p}\right)$, where $p \sim \mathbf{Be}(\mu, \nu)$. Thus, simulate $p_i \sim \mathbf{Be}(\mu, \nu)$, compute $\phi_i = \mathrm{logit}(p_i) - \log(2)$, and set $\gamma_i = \dfrac{e^{\phi_i}}{1 + e^{\phi_i}}$, $i = 1, \ldots, M$.

(ii) Let $\gamma = \dfrac{1 - \pi}{1 + \pi}$. We show in Appendix 3 that $\pi \sim \mathbf{Be}(\nu, \mu)$. Thus, simulate $\pi_i \sim \mathbf{Be}(\nu, \mu)$ and set $\gamma_i = \dfrac{1 - \pi_i}{1 + \pi_i}$, $i = 1, \ldots, M$.

We now focus on the joint marginal posterior distribution of (U, V) obtained under Jeffreys' prior

$$\begin{aligned} f(u, v \,|\, D) &\propto (u + rv)^{1/2} \frac{u^{m_{10}+m_{20}-1/2}(1-u)^{m_{00}-1/2}}{\mathbf{B}(m_{10} + m_{20} + 1/2, m_{00} + 1/2)} \\ &\times \frac{v^{m_{11}+m_{21}-1/2}(1-v)^{m_{01}-1/2}}{\mathbf{B}(m_{11} + m_{21} + 1/2, m_{01} + 1/2)}, \end{aligned}$$

which is independent of γ. To simulate M observations (u_i, v_i), $i = 1, \cdots, M$, we proceed as follows:

(a) Simulate independent observations (u_i, v_i), $i = 1, \cdots, M$, with $u_i \sim \mathbf{Be}\big(m_{10} + m_{20} + 1/2, m_{00} + 1/2\big)$ and $v_i \sim \mathbf{Be}\big(m_{11} + m_{21} + 1/2, m_{01} + 1/2\big)$.

(b) Compute the weights $w_i = (u_i + rv_i)^{1/2}$, $i = 1, \cdots, M$.

(c) Use the acceptance/rejection sampling method: Simulate $\xi_i \sim U(0, 1)$ and accept the pair (u_i, v_i) only if $\xi_i < w_i/(1 + r)$.

(d) Or use the importance sampling method, where all the pairs (u_i, v_i) are accepted and use the weights w_i to correct for the bias in the computation of posterior mean and quantiles.

Under the reference prior, we simulate independent observations (u_i, v_i), $i = 1, \cdots, M$, with $u_i \sim \mathbf{Be}\big(m_{10} + m_{20} + 1/2, m_{00} + 1/2\big)$ and $v_i \sim \mathbf{Be}\big(m_{11} + m_{21} + 1/2, m_{01} + 1/2\big)$. Having simulated a triplet (γ_i, U_i, V_i), we compute $\lambda_0^i = U_i/(1+\gamma_i)$ and $\lambda_1^i = V_i/(1+\gamma_i)$ as well as the risk difference, $\Delta_i = \dfrac{(V_i - U_i)}{(1 + \gamma_i)}$, the risk ratio, $R_i = \dfrac{V_i}{U_i}$ (does not depend on γ), and the odds ratio, $\psi_i = \dfrac{V_i\big[1 + \gamma_i - U_i\big]}{U_i\big[1 + \gamma_i - V_i\big]}$. These simulated values are in turn used to compute posterior probabilities and Bayesian credible intervals such as equal-tailed intervals and highest posterior density (HPD) intervals. Bayesian HPD intervals are the shortest intervals containing the parameter of interest with the desired posterior coverage probability. They are more desirable than the commonly used equal-tailed intervals when the posterior distribution is highly skewed, but are more difficult to compute. Chen and Shao (1999) develop the Monte Carlo method to compute the HPD intervals. In their paper, they also discussed how to compute Monte-Carlo-based Bayesian credible intervals under importance sampling.

3.5 Marginal Predictive Distribution and Bayes Factor

In this section, we derive the marginal predictive distribution and the Bayes factor under Jeffreys' prior and Bernardo's prior. For simplicity and clarity of the presentation, we work with the parameterization (γ, U, V). In addition, we derive a single Bayes factor formula for these two priors. To accomplish this single formulation, we use a family of prior distributions that encapsulates both Jeffreys' prior and the reference prior as special cases.

3.5.1 H_0: $\lambda_0 = \lambda_1$ versus H_1: $\lambda_1 \neq \lambda_0$

Consider the hypotheses H_0: $\lambda_0 = \lambda_1 = \lambda$ and H_1: $\lambda_1 \neq \lambda_0$ or equivalently H_0: $U = V = \theta$ against H_1: $U \neq V$. Under H_1, we consider the family of prior distributions

$$
\begin{aligned}
&\pi_{H_1}\big(\gamma, u, v\big) \\
&= \frac{1}{K} \frac{2^{\frac{1}{2}}}{\mathbf{B}(\frac{1}{2}, \frac{1}{2})} \frac{\gamma^{\frac{1}{2}-1}(1 - \gamma)^{\frac{1}{2}-1}}{(1 + \gamma)} (u + rv)^d \frac{u^{\frac{1}{2}-1}(1 - u)^{\frac{1}{2}-1}}{\mathbf{B}(\frac{1}{2}, \frac{1}{2})} \frac{v^{\frac{1}{2}-1}(1 - v)^{\frac{1}{2}-1}}{\mathbf{B}(\frac{1}{2}, \frac{1}{2})},
\end{aligned}
$$

where K is the normalizing constant and $0 < \gamma, u, v < 1$. Note that when $d = 0$, $K = 1$. Two choices of d are of interest: $d = 0$ corresponding to the reference prior and $d = 1/2$ corresponding to Jeffreys' prior. The marginal predictive distribution under H_1 is

$$
\begin{aligned}
p_{H_1}&(m_{10}, m_{20}, m_{11}, m_{21}) \\
&= \frac{1}{K} p(m_{10}, m_{20}, m_{11}, m_{21}) \int_0^1 \int_0^1 (u + rv)^d \frac{u^{m_{10}+m_{20}+\frac{1}{2}-1}(1-u)^{m_{00}+\frac{1}{2}-1}}{\mathbf{B}\left(m_{10}+m_{20}+\frac{1}{2}, m_{00}+\frac{1}{2}\right)} \\
&\quad \times \frac{v^{m_{11}+m_{21}+\frac{1}{2}-1}(1-v)^{m_{01}+\frac{1}{2}-1}}{\mathbf{B}\left(m_{11}+m_{21}+\frac{1}{2}, m_{01}+\frac{1}{2}\right)} dv\, du,
\end{aligned}
$$

where

$$
\begin{aligned}
p(m_{10}, m_{20},&m_{11}, m_{21}) = \binom{m_{+0}}{m_{00}, m_{10}, m_{20}}\binom{m_{+1}}{m_{01}, m_{11}, m_{21}}\frac{\mathbf{B}\left(m_{1+}+\frac{1}{2}, m_{2+}+\frac{1}{2}\right)}{\mathbf{B}\left(\frac{1}{2}, \frac{1}{2}\right)} \\
&\times \frac{\mathbf{B}\left(m_{10}+m_{20}+\frac{1}{2}, m_{00}+\frac{1}{2}\right)}{\mathbf{B}\left(\frac{1}{2}, \frac{1}{2}\right)}\frac{\mathbf{B}\left(m_{11}+m_{21}+\frac{1}{2}, m_{01}+\frac{1}{2}\right)}{\mathbf{B}\left(\frac{1}{2}, \frac{1}{2}\right)}.
\end{aligned}
$$

Under H_0, the likelihood reduces to

$$
L(\gamma, \theta) = \left\{\prod_{i=0}^1 \binom{m_{+i}}{m_{0i}, m_{1i}, m_{2i}}\right\} 2^{m_{1+}} \frac{\gamma^{m_{1+}}(1-\gamma)^{m_{2+}}}{(1+\gamma)^{m_{1+}+m_{2+}}} \theta^{m_{1+}+m_{2+}}(1-\theta)^{m_{0+}},
$$

where $\theta = (1+\gamma)\lambda$. Jeffreys' and Bernardo's priors belong to the family of priors

$$
\pi_{H_0}(\gamma, \theta) = \frac{2^{\frac{1}{2}}}{\mathbf{B}(\frac{1}{2}, \frac{1}{2})}\frac{\gamma^{\frac{1}{2}-1}(1-\gamma)^{\frac{1}{2}-1}}{(1+\gamma)}\frac{\theta^{a-1}(1-\theta)^{\frac{1}{2}-1}}{\mathbf{B}(a, \frac{1}{2})}, \quad 0 < \gamma, \theta < 1.
$$

Thus, the resulting marginal predictive distribution is

$$
\begin{aligned}
p_{H_0}&(m_{10}, m_{20}, m_{11}, m_{21}) \\
&= \binom{m_{+0}}{m_{00}, m_{10}, m_{20}}\binom{m_{+1}}{m_{01}, m_{11}, m_{21}}\frac{\mathbf{B}\left(m_{1+}+\frac{1}{2}, m_{2+}+\frac{1}{2}\right)}{\mathbf{B}\left(\frac{1}{2}, \frac{1}{2}\right)} \\
&\quad \times \frac{\mathbf{B}\left(m_{2+}+m_{1+}+a, m_{0+}+\frac{1}{2}\right)}{\mathbf{B}\left(a, \frac{1}{2}\right)}.
\end{aligned}
$$

The ratio of these two marginal predictive distributions, BF_{01}^λ, under the condition $P(H_1) = P(H_0) = \frac{1}{2}$ (the Bayes factor for testing H_0 vs H_1) satisfies

$$
\begin{aligned}
\frac{1}{BF_\lambda} &= \frac{\mathbf{B}\left(m_{10}+m_{20}+\frac{1}{2}, m_{00}+\frac{1}{2}\right)\mathbf{B}\left(m_{11}+m_{21}+\frac{1}{2}, m_{01}+\frac{1}{2}\right)\mathbf{B}\left(a, \frac{1}{2}\right)}{\mathbf{B}\left(m_{2+}+m_{1+}+a, m_{0+}+\frac{1}{2}\right)\mathbf{B}\left(\frac{1}{2}, \frac{1}{2}\right)\mathbf{B}\left(\frac{1}{2}, \frac{1}{2}\right)} \\
&\quad \times \int_0^1\int_0^1 \frac{(u+rv)^d}{K}\frac{u^{m_{10}+m_{20}+\frac{1}{2}-1}(1-u)^{m_{00}+\frac{1}{2}-1}}{\mathbf{B}(m_{10}+m_{20}+\frac{1}{2}, m_{00}+\frac{1}{2})}\frac{v^{m_{11}+m_{21}+\frac{1}{2}-1}(1-v)^{m_{01}+\frac{1}{2}-1}}{\mathbf{B}(m_{11}+m_{21}+\frac{1}{2}, m_{01}+\frac{1}{2})}dv\,du.
\end{aligned}
$$

Under Jeffreys' prior, the constant K and the integral term in the Bayes factor are computed using computer simulation. Under the reference prior, the integral term disappears and the Bayes factor is computed exactly using only the Beta functions.

3.5.2 H_0^*: $\gamma_1 = \gamma_0$ versus H_1^*: $\gamma_1 \neq \gamma_0$

One of the statements made in Dallal's model is that the parameter γ is constant. As discussed earlier, this assumption can be relaxed to $P(Z_{ijk} = 1 \mid Z_{ij(3-k)} = 1) = 1 - \gamma_i$, giving rise to the full or saturated model. Therefore, it is important to test the hypothesis H_0^*: $\gamma_1 = \gamma_0 = \gamma$ (Dallal's reduced model) versus the alternative hypothesis H_1^*: $\gamma_1 \neq \gamma_0$ (Dallal's full model). Under H_1^*, U and V are redefined as follows: $U = (1 + \gamma_0)\lambda_0$ and $V = (1 + \gamma_1)\lambda_1$. Under H_0^*, the prior is $\pi_{H_1}(\gamma, u, v)$ defined in Section 3.5.1. Under H_1^*, the family of priors under consideration is

$$
\pi_{H_1^*}(\gamma_0, \gamma_1, u, v) = \frac{2^{\frac{1}{2}}\gamma_0^{\frac{1}{2}-1}(1-\gamma_0)^{\frac{1}{2}-1}}{\mathbf{B}(\frac{1}{2},\frac{1}{2})(1+\gamma_0)} \frac{2^{\frac{1}{2}}\gamma_1^{\frac{1}{2}-1}(1-\gamma_1)^{\frac{1}{2}-1}}{\mathbf{B}(\frac{1}{2},\frac{1}{2})(1+\gamma_1)} \frac{u^{a_0-1}(1-u)^{\frac{1}{2}-1}}{\mathbf{B}(a_0,\frac{1}{2})}
$$
$$
\times \frac{v^{a_1-1}(1-v)^{\frac{1}{2}-1}}{\mathbf{B}(a_1,\frac{1}{2})}, \qquad 0 < \gamma_0, \gamma_1, u, v < 1.
$$

The resulting marginal predictive distribution is

$$
p_{H_1^*}(m_{10}, m_{20}, m_{11}, m_{21}) = \binom{m_{+0}}{m_{00}, m_{10}, m_{20}} \binom{m_{+1}}{m_{01}, m_{11}, m_{21}} \frac{\mathbf{B}(m_{10} + \frac{1}{2}, m_{20} + \frac{1}{2})}{\mathbf{B}(\frac{1}{2},\frac{1}{2})}
$$
$$
\times \frac{\mathbf{B}(m_{11} + \frac{1}{2}, m_{21} + \frac{1}{2})}{\mathbf{B}(\frac{1}{2},\frac{1}{2})} \frac{\mathbf{B}(m_{10} + m_{20} + a_0, m_{00} + \frac{1}{2})}{\mathbf{B}(a_0,\frac{1}{2})}
$$
$$
\times \frac{\mathbf{B}(m_{11} + m_{21} + a_1, m_{01} + \frac{1}{2})}{\mathbf{B}(a_1,\frac{1}{2})}.
$$

We are only concerned with two sets of parameters choices: $d = 1/2, a_0 = a_1 = 1$ used in Jeffreys' prior and $d = 0, a_0 = a_1 = 1/2$ used in the reference prior.

The Bayes factor for testing H_0^* vs H_1^* under the condition $P(H_1) = P(H_0) = \frac{1}{2}$ is

$$
BF_\gamma = \frac{p_{H_1}(m_{10}, m_{20}, m_{11}, m_{21})}{p_{H_1^*}(m_{10}, m_{20}, m_{11}, m_{21})}
$$
$$
= \frac{\mathbf{B}(m_{1+} + \frac{1}{2}, m_{2+} + \frac{1}{2})\mathbf{B}(a_0,\frac{1}{2})\mathbf{B}(a_1,\frac{1}{2})}{\mathbf{B}(m_{10} + \frac{1}{2}, m_{20} + \frac{1}{2})\mathbf{B}(m_{11} + \frac{1}{2}, m_{21} + \frac{1}{2})\mathbf{B}(\frac{1}{2},\frac{1}{2})}
$$
$$
\times \frac{\mathbf{B}(m_{10} + m_{20} + \frac{1}{2}, m_{00} + \frac{1}{2})\mathbf{B}(m_{11} + m_{21} + \frac{1}{2}, m_{01} + \frac{1}{2})}{\mathbf{B}(m_{10} + m_{20} + a_0, m_{00} + \frac{1}{2})\mathbf{B}(m_{11} + m_{21} + a_1, m_{01} + \frac{1}{2})}
$$
$$
\times \int_0^1 \int_0^1 \left\{ \frac{(u+rv)^d}{K} \frac{u^{m_{10}+m_{20}+\frac{1}{2}-1}(1-u)^{m_{00}+\frac{1}{2}-1}}{\mathbf{B}(m_{10} + m_{20} + \frac{1}{2}, m_{00} + \frac{1}{2})} \right.
$$
$$
\left. \times \frac{v^{m_{11}+m_{21}+\frac{1}{2}-1}(1-v)^{m_{01}+\frac{1}{2}-1}}{\mathbf{B}(m_{11} + m_{21} + \frac{1}{2}, m_{01} + \frac{1}{2})} \right\} dv\,du.
$$

Under Jeffreys' prior, BF_γ is computed using computer simulation while under the reference prior it is computed exactly.

4 Comparisons of Bayesian and Frequentist Intervals: An Empirical Study

In this section, we investigate small, moderate and large-sample performances of frequentist confidence intervals (FCIs) and Bayesian credible intervals (BCIs) under three criteria. For a set values for the model parameters, 10,000 3×2 bilateral data tables are generated from the product of trinomial distributions under a balanced design. The essence of these criteria rely on the principle that good FCIs (Wald FCIs described in Appendix 1 of the Supplementary Web Materials) or good HPD BCIs should have their true coverage close to or preferably larger than the nominal value. Indeed, FCIs and BCIs with deflated true coverage are recommended against. Lengths of the intervals must also be considered. We use the three following criteria:

(i) the expected true coverage probability (ETCP) of the interval $\left(\widehat{\Delta}_L, \widehat{\Delta}_U\right)$ for Δ, $P\left(\widehat{\Delta}_L \leq \Delta \leq \widehat{\Delta}_U\right)$, in repeated sampling;

(ii) the expected width (EWCI) of the interval of $\left(\widehat{\Delta}_L, \widehat{\Delta}_U\right)$ for Δ, $\widehat{\Delta}_U - \widehat{\Delta}_L$, in repeated sampling; and

(iii) the expected mean square error (MSE) that reflects a compromise between bias and precision, in repeated sampling.

Although these criteria are defined in terms of Δ, we also examine the behaviors of these criteria for $(\gamma, \lambda_0, \lambda_1)$ as well. For the case of the MSE, we go further by adding the three MSEs corresponding to $(\gamma, \lambda_0, \lambda_1)$ to obtain a global measure of MSE. Four equal sample size scenarios are chosen: $m_{+0} = m_{+1} = m = 10, 25, 50, 100$ to reflect small, moderate and large sample size situations. For symmetry, we only consider cases where Δ is non-negative. More specifically, we examine cases with $\Delta = \Delta_h = h/10$, $h \in \{0, 1, 2, 3, 4, 5, 6, 7, 8, 9\}$. Each choice of Δ implies the constraint: $0 < \gamma < \gamma_{h,\max} = \min(1, 1/\Delta_h - 1)$. We then choose a grid of γ points: $\gamma_{hj} = j\gamma_{h,\max}/10$ with $j = 1, 2, \ldots, 9$. These values are meant to capture a wide range of behaviours of the conditional probability of an occurrence of a particular characteristic at one site given an occurrence of that characteristic at the other site in the range $(1 - \gamma_{h,\max}, 1)$. Then, set $\lambda_{hj,\max} = \dfrac{1}{1 + \gamma_{hj}} - \Delta_h$. For the pair (λ_0, λ_1), we select the values: $\lambda_{0hjk} = k\lambda_{hj,\max}/10$ with $k = 1, 2, \ldots, 9$ and $\lambda_{1hjk} = \lambda_{0hjk} + \Delta_h$. Hence, for each sample size and Δ_h, we compute the three criterion functions for 81 combinations of the triplets $(\gamma, \lambda_0, \lambda_1)$. In the Bayesian framework, we examine HPD intervals under the uniform, Jeffreys', and reference priors.

The probability of obtaining degenerate results in the frequentist framework (non-estimable model parameters or model parameters on the boundary of the parameter space or parameters with a zero variance) is relatively high in smaller samples, and even higher when combined with large and small γ values. These cases are eliminated from the frequentist calculations. The five tables in Appendix 2 of the Supplementary Web Materials give a summary of results of the simulation study. In each cell, we

compute two numbers: the proportion of empirical coverages within 0.01 of the nominal coverage and the proportion of empirical coverages above -0.02 of the nominal coverage. The latter summary carries out more value than the former one. The findings for the ETCP criterion are summarized as follows.

(a) For $\Delta = 0$, Bayesian HPD intervals perform similarly for moderate and large sample sizes ($m = 50, 100$) and the proportions of coverages above -0.02 of the nominal coverage are close to 100% for λ_0, λ_1 and Δ. This finding actually holds true for $\Delta \leq 0.4$.

(b) Wald FCIs perform poorly for estimating λ_0 and λ_1 when $m = 10, 25$ and $\Delta \leq 0.3$.

(c) Overall, in terms of coverage probability, the uniform distribution seems to perform better than the other methods when $\Delta \leq 0.5$. When $\Delta \geq 0.6$, Jeffreys' prior and the reference prior perform better when estimating λ_0, λ_1 and Δ.

(d) When it comes to estimating γ, the uniform prior outperforms the other methods regardless of the nominal value of Δ.

(e) In general, Jeffreys' prior and the reference prior tend to give similar results regardless of the nominal value of Δ.

A summary of the findings for the MSE criterion is given as follows.

(a) Jeffreys' prior and the reference prior perform similarly regardless of the nominal value of Δ. The MSEs for Δ are scattered around the line $y = x$, with increasing deviations as n gets smaller. As Δ increases, the deviations from the 45 degree line also increase with a slim advantage of Jeffreys' prior when $\Delta > 0.5$. See Figures 1 and 2. The same pattern is observed with the global measure of MSE obtained by adding the MSEs for γ, λ_0 and λ_1.

(b) Jeffreys' prior and the uniform prior have equivalent properties for moderate and large sample sizes when $\Delta \leq 0.6$. However, when $\Delta \geq 0.7$, the superiority of Jeffreys' prior is highly evident.

(c) Wald FCIs perform worst when $\Delta \leq 0.6$, with differences worsening as n gets smaller. This behavior is reversed when $\Delta \geq 0.7$. See Figures 1 and 2.

(d) In terms of the MSEs corresponding to γ, all the Bayesian approaches perform better than Wald's approach when $\Delta \leq 0.8$.

The findings for the EWCI criterion are the following.

(a) Jeffreys' prior and the reference prior give similar results when estimating Δ. See Figure 4. The reference prior tends to be better than the uniform prior when $\Delta \geq 0.6$ and inferior when $\Delta \leq 0.5$. The Wald FCI is the worst when $\Delta \leq 0.6$ and the best when $\Delta \geq 0.7$. See Figure 3.

(b) Wald FCIs perform worst when estimating γ. The uniform prior is no better than Jeffreys' prior with a slight edge to Jeffreys' prior when the sample size is small.
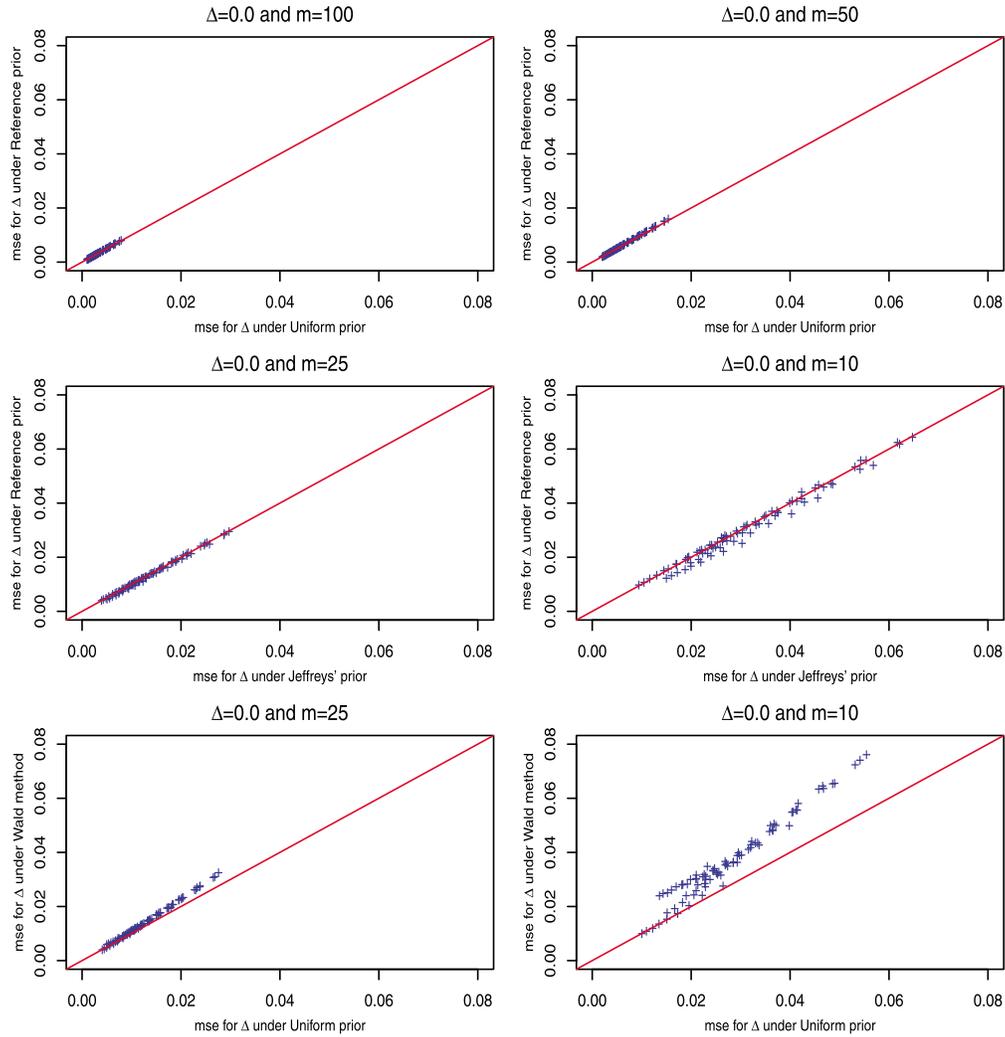
Figure 1: Graphs of the 81 empirical MSEs for Δ generated from the case $\Delta = 0$.

5 Case Studies

5.1 Bayesian Analysis of Bilateral Data with Sparse Data

Mandel et al. (1982) considered a double-blind randomized clinical trial which compared the antibiotics Cefaclor and Amoxicillin for the treatment of otitis media with effusion (OME). Among a total of 214 participants in the trial, 11 children were at least six years old and underwent bilateral tympanocentesis prior to randomization into one of two groups (Cefaclor or Amoxicillin). Children in each treatment group received a 14-
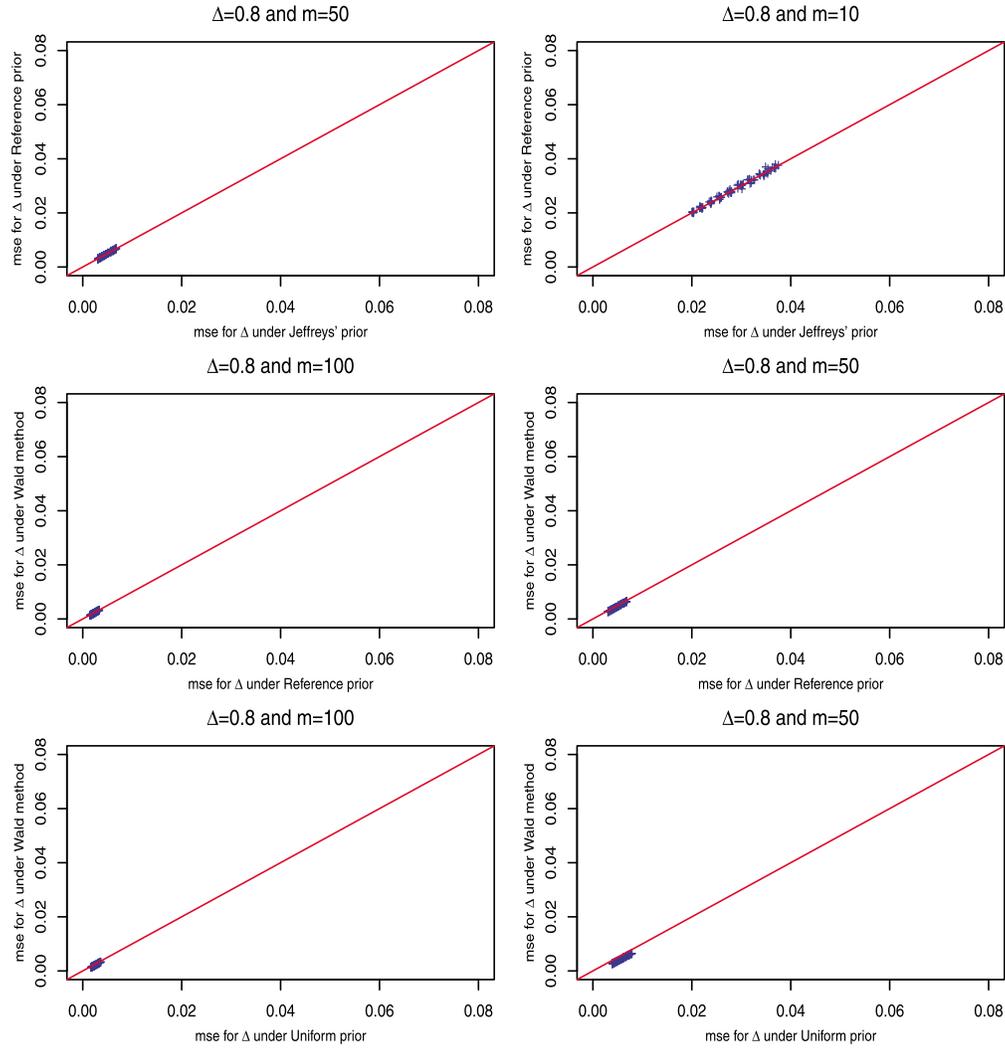
Figure 2: Graphs of the 81 of empirical MSEs for Δ generated from case $\Delta = 0.8$.

day course of treatment with one of the antibiotics and dichotomous ear outcomes were determined (i.e., cured or not-cured) and recorded. Table 2 provides a summary of the data collected. The primary goal of this investigation is to test if the cure rates were identical between Cefaclor and Amoxicillin. A further goal is to estimate the size of the difference of the percentage change, $R - 1$, in the performance of the two medications. This example was discussed in Tang et al. (2008) under Rosner's model. They obtained $\widehat{\lambda}_0 = 0.875$ and $\widehat{\lambda}_1 = 0.857$. They also found that there is no evidence to reject the null hypothesis of equal cure rates.
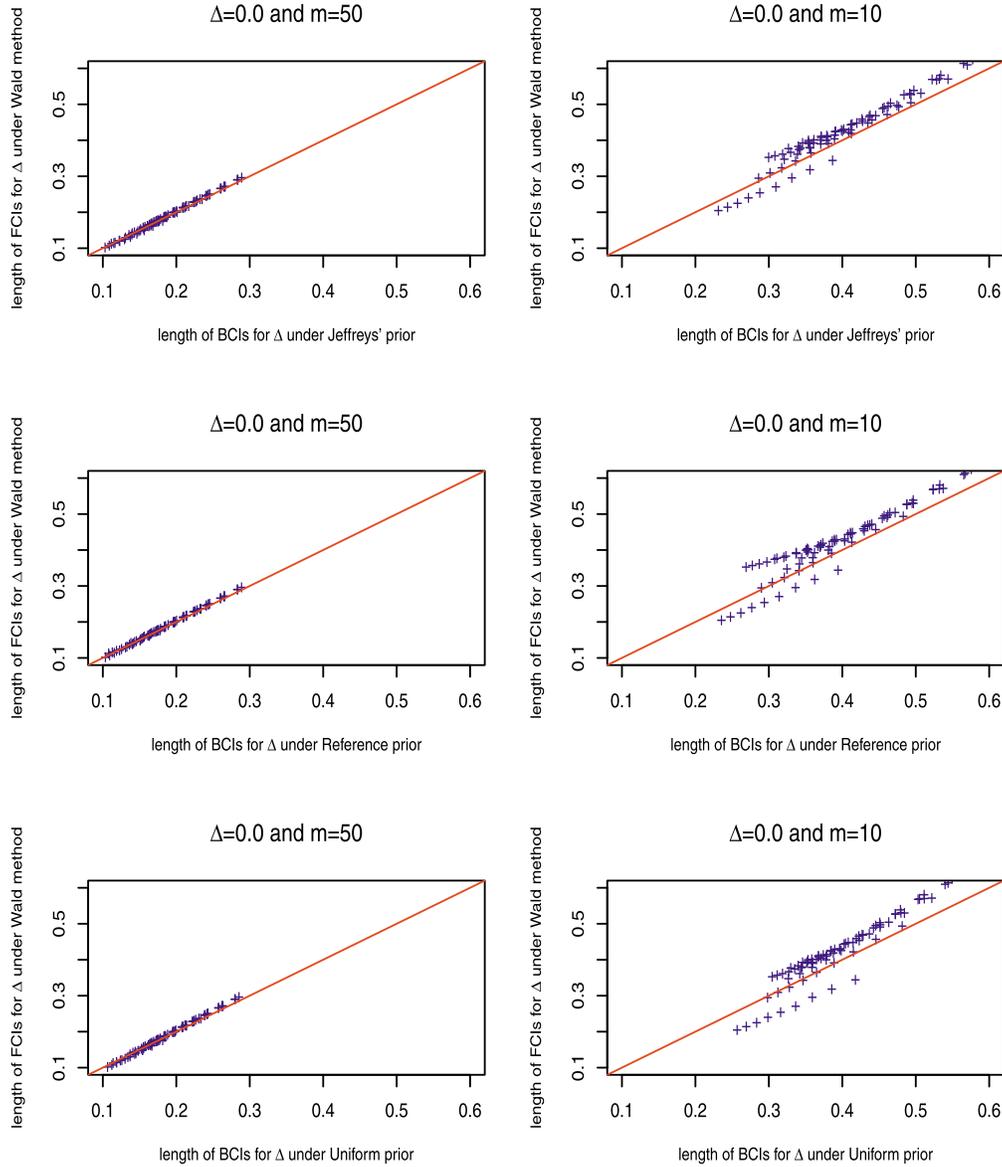
Figure 3: Graph of the 81 empirical lengths of 90% HPD intervals generated from the case $\Delta = 0.0$.

Two striking features characterize this data. (i) The total sample sizes in the Cefaclor and Amoxicillin groups are extremely small. (ii) Table 2 is sparse with a zero cell in each group. As a result, the normal approximation used in classical analysis does not apply. In addition, the maximum likelihood estimates (MLEs) of Dallal's reduced
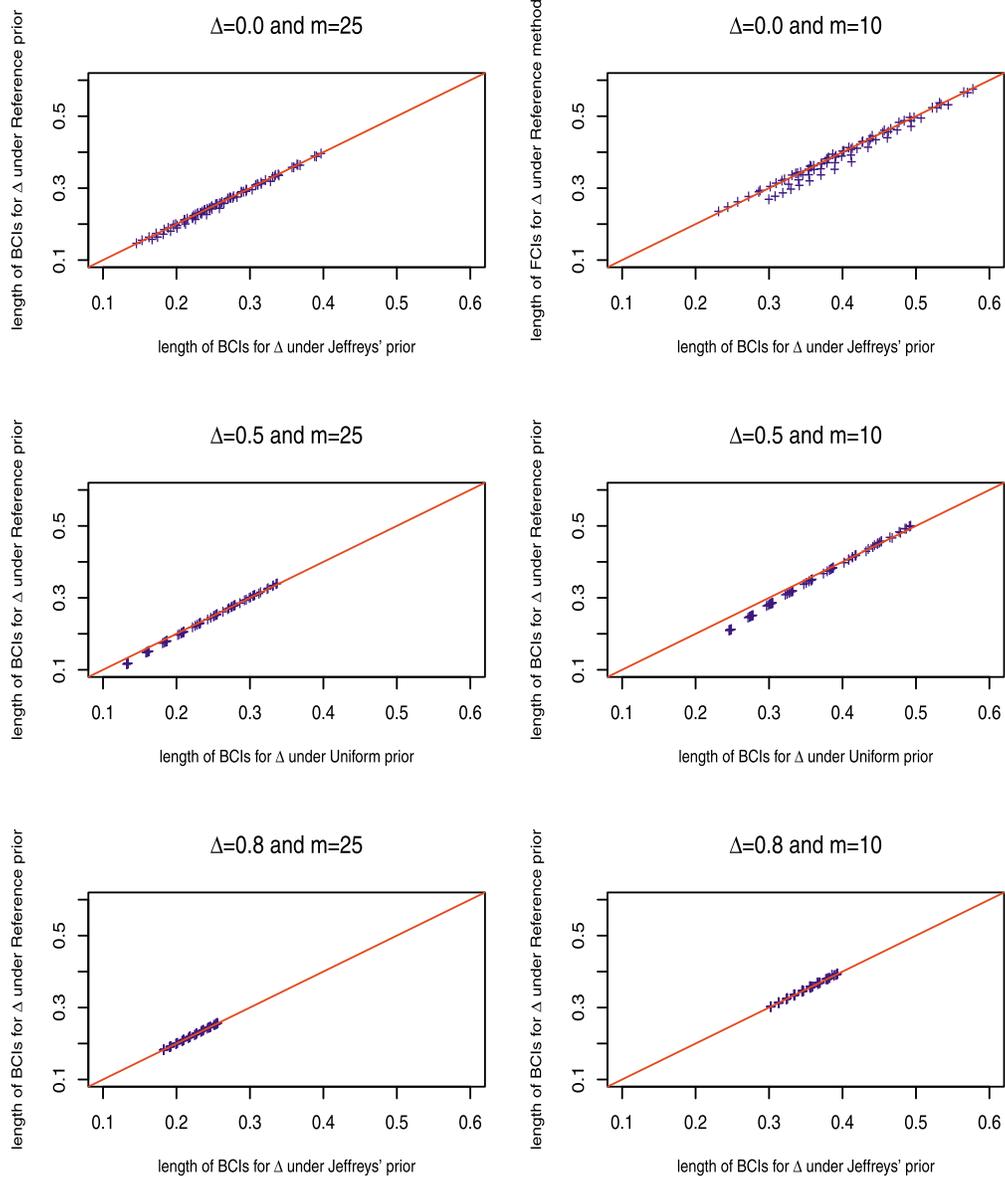
Figure 4: Graph of the 81 empirical lengths of 90% HPD intervals generated from the case $\Delta = 0.0, 0.5, 0.8$.

and saturated models sit on the boundary of the parameter space (leading to success probabilities not truly allowed by the product trinomial model). It is impossible to carry out frequentist inference or apply a likelihood-based model selection procedure. In this situation, a common ad-hoc adjustment is to add 1/2 to each cell count. A problem

Table 2: OME status after 14 days of Cefaclor or Amoxicillin treatments.

Number of ears with	Treatment Group	
OME being cured	Amoxicillin	Cefaclor
0	1	0
1	0	1
2	6	3
Total	**7**	**4**

with this ad-hoc adjustment is that the total sample sizes are not integer numbers. The normal approximation still does not apply despite this adjustment. So the Bayesian methodology appears here to be one of the few alternatives.

Table 3: MLEs under Dallal's reduced and saturated models.

Reduced Model							
No Adjustments							
U	V	γ	λ_0	λ_1	Δ	R	ψ
1	6/7	1/19	0.95	57/70	-19/140	6/7	3/13
Ad-hoc Adjustment							
U	V	γ	λ_0	λ_1	Δ	R	ψ
10/11	14/17	1/11	5/6	77/102	-4/51	77/85	77/125

Saturated Model								
No Adjustments								
U	V	γ_0	γ_1	λ_0	λ_1	Δ	R	ψ
1	6/7	1/7	0	0.875	6/7	-1/56	48/49	6/7
Ad-hoc Adjustment								
U	V	γ_0	γ_1	λ_0	λ_1	Δ	R	ψ
10/11	14/17	3/17	1/27	17/22	27/34	4/187	297/289	135/119

Bayesian posterior estimates and 95% HPD intervals for Dallal's model and the saturated model based on Jeffreys', the reference, and the uniform priors and 100,000 iterations are summarized in Tables 4 and 5. Under these three priors, the posterior means of U are far away from the parameter space boundaries as indicated by the non-zero median estimates (not provided for obvious reasons). The 95% HPD intervals for R under the uniform prior tend to be larger than those under Jeffreys' prior or the reference prior. In addition, the uniform prior seems to perform the worst in terms of the deviance information criterion (DIC) while Jeffreys' prior and the reference prior seem to perform similarly. The risk difference is essentially zero ($BF_\lambda^J = 1.965$ and $P(\Delta > 0|D) = 0.550$; $BF_\lambda^R = 1.818$ and $P(\Delta > 0|D) = 0.541$) and the two cure rates themselves are very high (above 75%). We retain the saturated model over Dallal's reduced model according to the DIC and $P(\gamma_1 - \gamma_0 < 0|D)$. However, the Bayes factors indicate minimal evidence against the null hypothesis $H_0^* : \gamma_1 = \gamma_0$ ($BF_\gamma^J = 0.682$ and $BF_\gamma^R = 1.052$). The 95% HPD interval for $\gamma_1 - \gamma_0$ also covers zero. According to the retained model, the conditional posterior probabilities of the cure rate at one site given

Table 4: Posterior estimates and credible intervals based on Dallal's model.

	mean	std	95% HPD		mean	std	95% HPD
Jeffreys' Prior							
$P(\Delta < 0\|D) = 0.739$, DIC=9.843, pD=1.613							
	mean	std	95% HPD		mean	std	95% HPD
U	0.904	0.119	(0.649, 1.000)	λ_1	0.764	0.125	(0.515, 0.970)
V	0.819	0.127	(0.570, 1.000)	Δ	-0.079	0.162	(-0.417, 0.265)
γ	0.076	0.061	(0.000, 0.198)	R	0.931	0.245	(0.468, 1.370)
λ_0	0.842	0.120	(0.597, 0.998)	ψ	1.013	2.052	(0.002, 3.423)
Bernardo's Prior							
$P(\Delta < 0\|D) = 0.737$, DIC=9.953, pD=1.631							
	mean	std	95% HPD		mean	std	95% HPD
U	0.899	0.124	(0.635, 1.000)	λ_1	0.756	0.128	(0.505, 0.969)
V	0.812	0.130	(0.559, 0.999)	Δ	-0.082	0.168	(-0.439, 0.261)
γ	0.077	0.062	(0.000, 0.199)	R	0.929	0.260	(0.469, 1.395)
λ_0	0.838	0.124	(0.583, 0.997)	ψ	1.030	2.166	(0.001, 3.486)
Uniform Prior							
$P(\Delta < 0\|D) = 0.640$, DIC=10.378, pD=1.316							
	mean	std	95% HPD		mean	std	95% HPD
U	0.833	0.141	(0.549, 1.000)	λ_1	0.713	0.127	(0.461, 0.935)
V	0.778	0.131	(0.524, 0.989)	Δ	-0.051	0.177	(-0.400, 0.317)
γ	0.095	0.066	(0.003, 0.224)	R	0.973	0.303	(0.453, 1.536)
λ_0	0.764	0.136	(0.491, 0.977)	ψ	1.200	1.766	(0.016, 3.796)

the other site was cured are very high and slightly higher in the Amoxicillin group, therefore this dependency cannot be ignored. There is also a noticeable discrepancy between the correlation coefficients for the Z_{ijk} variables for the two treatment groups, $1 - \dfrac{\gamma_i}{1 - \lambda_i}$, $i = 0, 1$.

5.2   Bayesian Analysis of Bilateral Data with Large Sample Data

Postlethwaite et al. (2008) considered a two-arm multi-centre double-blind randomized trial where 168 diffuse scleroderma patients are randomized to one of two groups to receive either oral native collagen at a dose of 500g/day or a similar appearing placebo. The total duration of the treatment phase was 12 months with an additional visit at month 15 for safety follow-up. Rheumatologists routinely examine both the left and right feet, forearms, hands, fingers, legs, thighs, and upper arms of the patient and assign a modified Rodnan Skin Score (MRSS) score between 0 and 3, that is 0 for normal, 1 for mild, 2 for moderate and 3 for severe skin thickening. The patient's improvement at each body part level is recorded. After consultation with rheumatologists, a patient has improved at a body part level if the MRSS at the end of the trial is either zero or has dropped by two units or more from baseline. The goal is to test whether there is a significant difference in the improvement rates between the two groups at each body part level. Table 6 reports an examplary set of results from the trial for the forearms.

Table 5: Posterior estimates and credible intervals based on the saturated model.

	mean	std	95% HPD		mean	std	95% HPD
Jeffreys' Prior
Jeffreys' Prior							
$P(\Delta > 0|D) = 0.550$, $P(\gamma_1 - \gamma_0 < 0|D) = 0.890$, DIC=8.680, pD=1.619							
	mean	std	95% HPD		mean	std	95% HPD
U	0.910	0.112	(0.670, 1.000)	Δ	0.021	0.179	(-0.342, 0.371)
V	0.824	0.123	(0.583, 0.998)	R	1.065	0.299	(0.548, 1.628)
γ_0	0.192	0.145	(0.000, 0.481)	ψ	2.633	7.094	(0.001, 8.849)
γ_1	0.039	0.055	(0.000, 0.151)	δ	-0.132	0.167	(-0.491, 0.200)
λ_0	0.773	0.128	(0.532, 0.988)	$\Delta\gamma$	-0.153	0.155	(-0.495, 0.114)
λ_1	0.795	0.125	(0.553, 0.993)				
Bernardo's Prior							
$P(\Delta > 0|D) = 0.541$, $P(\gamma_1 - \gamma_0 < 0|D) = 0.889$, DIC=8.858, pD=1.645							
	mean	std	95% HPD		mean	std	95% HPD
U	0.900	0.122	(0.638, 1.000)	Δ	0.019	0.186	(-0.361, 0.393)
V	0.813	0.129	(0.560, 0.999)	R	1.067	0.326	(0.508, 1.667)
γ_0	0.193	0.145	(0.000, 0.484)	ψ	2.574	6.512	(0.004, 8.772)
γ_1	0.040	0.055	(0.000, 0.153)	δ	-0.135	0.176	(-0.502, 0.221)
λ_0	0.765	0.134	(0.508, 0.988)	$\Delta\gamma$	-0.153	0.155	(-0.506, 0.106)
λ_1	0.784	0.130	(0.531, 0.989)				
Uniform Prior							
$P(\Delta > 0|D) = 0.583$, $P(\gamma_1 - \gamma_0 < 0|D) = 0.854$, DIC=10.119, pD=1.352							
	mean	std	95% HPD		mean	std	95% HPD
U	0.833	0.141	(0.548, 1.000)	Δ	0.040	0.192	(-0.339, 0.418)
V	0.777	0.132	(0.522, 0.989)	R	1.116	0.386	(0.476, 1.831)
γ_0	0.231	0.148	(0.007, 0.521)	ψ	2.161	3.727	(0.022, 6.814)
γ_1	0.075	0.073	(0.000, 0.224)	δ	-0.110	0.186	(-0.484, 0.267)
λ_0	0.686	0.140	(0.414, 0.938)	$\Delta\gamma$	-0.157	0.165	(-0.515, 0.142)
λ_1	0.725	0.131	(0.470, 0.956)				

In blocks 1 and 2 of Table 7, we provide Bayesian posterior estimates and credible intervals for Dallal's model based on Jeffreys' and Bernardo's priors. The results are based on 100,000 posterior simulations. In block 3 of Table 7, we provide frequentist MLEs, Wald FCIs, Aikaike information criterion (AIC) and Bayesian information criterion (BIC), along with large-sample χ^2 test for $H_0 : \lambda_0 = \lambda_1$ and $H_0^* : \gamma_1 = \gamma_0$. For this data, the total sample size in each group is moderate. Although four of the cells have counts less than 5, the tallies that matter here are the subtotals, $m_{1+} = 7, m_{2+} = 9, m_{10} + m_{20} = 6, m_{00} = 55, m_{11} + m_{21} = 10, m_{01} = 36$, which are all greater than 5. We provide only the results for Dallal's reduced model. Indeed, Bayes factors indicate the null hypothesis, $H_0^* : \gamma_1 = \gamma_0$, is supported. In this example, the treatment cure rate has decreased the disease risk by two fold. The risk of disease in both treatment and control groups remain high (above 80%). The null hypothesis of equality of the treatment cure rates, $H_0 : \lambda_0 = \lambda_1$ is supported by our analysis. Overall Dallal's model and the saturated model give similar results and there is no difference between using Jeffreys' prior (e.g., $\widehat{R} = 2.479$ and BCI: (0.640, 5.007))

Table 6: Number of scleroderma patients whose forearm MRSS decreased by 2 or 3, or has 0 MRSS at month 15.

| Number of forearms | Treatment Group | |
with improvement	Collagen	Placebo
0	36	55
1	4	3
2	6	3
Total	**46**	**61**

Table 7: Posterior estimates and credible intervals as well as frequentist MLEs and confidence intervals based on Dallal's model.

| **Jeffreys' Prior** | | | | | | | |
| $P(\Delta > 0\|D) = 0.956$, DIC=18.563, pD=2.878, $BF_\lambda = 1.607$, $BF_\gamma = 3.733$ | | | | | | | |
	mean	std	95% HPD		mean	std	95% HPD
U	0.107	0.039	(0.037, 0.186)	λ_1	0.178	0.049	(0.087, 0.277)
V	0.229	0.061	(0.114, 0.348)	Δ	0.095	0.057	(-0.017, 0.208)
γ	0.290	0.099	(0.109, 0.486)	R	2.479	1.338	(0.640, 5.007)
λ_0	0.084	0.031	(0.028, 0.147)	ψ	2.855	1.746	(0.566, 6.124)
Bernardo's Prior							
$P(\Delta > 0\|D) = 0.957$, DIC=18.523, pD=2.882, $BF_\lambda = 1.526$, $BF_\gamma = 2.368$							
	mean	std	95% HPD		mean	std	95% HPD
U	0.104	0.038	(0.037, 0.182)	λ_1	0.174	0.049	(0.085, 0.272)
V	0.223	0.060	(0.111, 0.341)	Δ	0.092	0.056	(-0.015, 0.204)
γ	0.291	0.099	(0.110, 0.487)	R	2.481	1.318	(0.630, 5.004)
λ_0	0.081	0.031	(0.027, 0.143)	ψ	2.846	1.707	(0.582, 6.115)
Likelihood							
AIC=18.712, BIC=26.730, pD=3, $\chi^2_\lambda = 2.897$, $\chi^2_\gamma = 0.152$							
	mle	std	95% CI		mle	std	95% CI
U	0.098	0.038	(0.024, 0.173)	λ_1	0.170	0.049	(0.073, 0.267)
V	0.217	0.061	(0.098, 0.337)	Δ	0.093	0.057	(-0.019, 0.205)
γ	0.280	0.102	(0.081, 0.479)	R	2.210	1.057	(0.866, 5.641)
λ_0	0.077	0.030	(0.017, 0.136)	ψ	2.458	1.323	(0.855, 7.062)

or Bernardo's prior (e.g., $\widehat{R} = 2.481$ and BCI: (0.630, 5.004)), although results from Bernardo's reference prior are easier to compute. Note that our posterior estimates and HPD intervals for the risk difference are in line with the results in Pei et al. (2010) obtained under the equal correlation model ($\widehat{\Delta} = 0.0970$, CI: $(-0.0214, 0.2217)$).

6 General Classes of Prior Distributions

The reference priors and the uniform prior discussed earlier can be embedded in the family of prior distributions

$$\pi(\gamma, \lambda_0, \lambda_1) = \frac{2^\alpha}{\mathbf{B}(\alpha, \beta)} \frac{\gamma^{\alpha-1}(1-\gamma)^{\beta-1}}{(1+\gamma)^{\alpha+\beta-a_0-a_1}} \frac{\lambda_0^{a_0-1} \left[1 - (1+\gamma)\lambda_0\right]^{b_0-1}}{\mathbf{B}(a_0, b_0)}$$

$$\frac{\lambda_1^{a_1-1} \left[1 - (1+\gamma)\lambda_1\right]^{b_1-1}}{\mathbf{B}(a_1, b_1)}, \qquad (\gamma, \lambda_0, \lambda_1) \in \Omega, \qquad (12)$$

which is equivalent to stating that

$$\pi(\gamma, u, v) = \frac{2^\alpha}{\mathbf{B}(\alpha, \beta)} \frac{\gamma^{\alpha-1}(1-\gamma)^{\beta-1}}{(1+\gamma)^{\alpha+\beta}} \frac{u^{a_0-1}(1-u)^{b_0-1}}{\mathbf{B}(a_0, b_0)} \frac{v^{a_1-1}(1-v)^{b_1-1}}{\mathbf{B}(a_1, b_1)}. \qquad (13)$$

Another representation of this class of prior distributions is through the following hierarchical model: (a) $\gamma \sim f(\gamma) = \dfrac{2^\alpha}{\mathbf{B}(\alpha, \beta)} \dfrac{\gamma^{\alpha-1}(1-\gamma)^{\beta-1}}{(1+\gamma)^{\alpha+\beta}}$ or equivalently $\dfrac{1-\gamma}{1+\gamma} \sim \mathbf{Be}(\beta, \alpha)$, (b) $\lambda_0|\gamma \sim \mathbf{Be}\left(a_0, b_0; 0, \dfrac{1}{1+\gamma}\right)$, and (c) $\lambda_1|\gamma \sim \mathbf{Be}\left(a_1, b_1; 0, \dfrac{1}{1+\gamma}\right)$, where $\mathbf{Be}(\alpha, \beta; l, u)$ stands for a Beta random variable with shape parameters α and β defined on the interval (l, u).

Jeffreys' prior distribution for the parameterization (γ, U, V) suggests a larger family of conjugate prior distributions for (γ, U, V), namely,

$$\pi(\gamma, u, v) \propto \frac{2^\alpha}{\mathbf{B}(\alpha, \beta)} \frac{\gamma^{\alpha-1}(1-\gamma)^{\beta-1}}{(1+\gamma)^{\alpha+\beta}} (u + rv)^{1/2} u^{a_0-1}(1-u)^{b_0-1} v^{a_1-1}(1-v)^{b_1-1},$$

with $0 < \gamma, u, v < 1$ and $\alpha, \beta, a_0, b_0, a_1, b_1 > 0$, which translates into the prior distribution

$$\pi(\gamma, \lambda_0, \lambda_1) \propto \frac{2^\alpha}{\mathbf{B}(\alpha, \beta)} \frac{\gamma^{\alpha-1}(1-\gamma)^{\beta-1}}{(1+\gamma)^{\alpha+\beta-a_0-a_1-d}} (\lambda_0 + r\lambda_1)^{1/2} \lambda_0^{a_0-1} \left[1 - (1+\gamma)\lambda_0\right]^{b_0-1}$$

$$\times \lambda_1^{a_1-1} \left[1 - (1+\gamma)\lambda_1\right]^{b_1-1}, \qquad (\gamma, \lambda_0, \lambda_1) \in \Omega. \qquad (14)$$

7 Concluding Remarks

Using the parameterization (γ, U, V), it can be deduced that $\Delta = \dfrac{V - U}{1 + \gamma}$. This result highlights a direct dependence of the risk difference on the nuisance parameter γ. This result also points out the main difference between the risk difference in 3×2 bilateral data and the risk difference, $V - U$, in an ordinary 2×2 table where one collects a single measurement per subject. In other words, the divisor $1 + \gamma$ is the term that connects the two disease risks in the bilateral data context. Indeed, according to the expression of the likelihood, $L(\gamma, U, V)$, given in Appendix 1, the parameters U and V can be interpreted as the proportions of cases with one or more body part(s) cured in the placebo and treatment groups. On the opposite side, λ_0 and λ_1 are interpreted as the proportions of body parts cured in the placebo and treatment groups. So unlike U and V, one individual can contribute twice in the computation of λ_0 and λ_1.

Table 8: Relevant summary statistics for the risk ratio.

Numbers of cured organs	Group	
	Treatment	Control
0	$m_{01} (1 - U)$	$m_{00} (1 - V)$
1 or 2	$m_{+1} - m_{01} (U)$	$m_{+0} - m_{00} (V)$

Another benefit of the parameterization (γ, U, V) is that it shows that the risk ratio, $R = \dfrac{\lambda_1}{\lambda_0} = \dfrac{V}{U}$, does not depend on the nuisance parameter γ. As a result, both frequentist and Bayesian inferences do not depend on γ and are easier to compute. Therefore, the risk ratio has a technical advantage on the risk difference. Moreover, the definition of R in 3×2 bilateral data coincides with the definition R from the 2×2 binary table in Table 8. Actually, the 3×2 bilateral table can be replaced by Table 8 when the focus is on R. For these reasons, our choice of the parameter in a bilateral data design is the risk ratio.

While there are numerous frequentist papers dealing with bilateral data, this work remains incomplete. For example, Dallal's model used in this paper has not been investigated in the frequentist literature although other models have and there are no Bayesian treatments of the problem. Although the risk ratio and the odds ratio are well established parameters in medical settings, they do not appear in the bilateral data literature. A clear advantage of the risk ratio over the commonly used risk difference is that inference does not involve the nuisance parameter γ. In addition, the risk ratio remains unchanged when going from an ordinary 2×2 binary table where all observations are independent to a 3×2 binary table where observations taken from the same subjects are correlated. The risk ratio and the odds ratio open the door for bilateral data to be studied under a prospective scheme or a retrospective scheme using an observational study paradigm. The presentation exposed here has taken into account all these inconveniences and has provided a broad discussion of the Bayesian framework both from the point of view of the tests of hypotheses as well as the estimation of the key model parameters. We have added a simulation study to empirically compare the effectiveness of Bayesian methods against themselves as well as frequentist methods in the context of small, moderate and large sample sizes and for a wide range of Δ values. For example, we have found that Jeffreys' prior and the reference prior tend to perform similarly. We have also found that frequentist methods tend to perform very poorly when Δ is small and the sample size is small or moderate. The uniform prior has the best overall property when it comes to estimating the parameter γ. We have concluded our work with two detailed case studies, one of which shows that it is impossible to carry out frequentist inference given that some of the parameters sit on the boundary of the parameter space or the normal approximation is not accurate. Our Bayesian framework works remarkably well in these situations as well as the large sample cases.

When subject level bilateral data with covariates are available, Dallal's regression model can be developed in order to incorporate covariates. As discussed in Section 3.2, γ, $U = (1 + \gamma)\lambda_0$, and $V = (1 + \gamma)\lambda_1$ are unconstrained and the parameter space is

(0,1) for each of these three transformed parameters. Therefore, a logistic regression model can be assumed for each of γ, U, and V. Consequently, Jeffreys' prior and the reference prior can be derived. However, the computational and theoretical properties of these priors need to be carefully examined. The development of Dallal's regression model deserves a future research project, which is currently under investigation.

Acknowledgments

Supplementary Material

Supplementary Web Materials for "Objective Bayesian Inference for Bilateral Data" (DOI: 10.1214/14-BA890SUPP; .pdf).

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Appendix 1: Derivation of Jeffreys' Prior

Set $U = (1 + \gamma)\lambda_0$ and $V = (1 + \gamma)\lambda_1$. Under this new parametrization, the parameter space reduces to the interval $[0, 1]$ for each of the three parameters. Theorem A.1 emphasizes the role of a reparametrization technique in obtaining Jeffreys' prior distribution in the original parametrization after having derived Jeffreys' prior in the reparametrized space.

Theorem   A.1 (Consistency   Under   Reparametrization).   *Consider   a   model* $\mathfrak{M} \equiv \{p(X|\theta), \mathbf{x} \in \mathcal{X}, \theta \in \Theta\}$ *and let* $\phi(\theta)$ *be an invertible transformation of* θ. *Then, the Jeffreys' prior corresponding to the parameter* ϕ, $\pi(\phi)$, *is that induced by the Jeffreys' prior density of* θ, $\pi(\theta)$. We prove Proposition 3.1 and 3.2 below.

Proof. As a function of (γ, U, V), the likelihood function simplifies to

$$L(\gamma, U, V) \propto \frac{\gamma^{m_{1+}}(1 - \gamma)^{m_{2+}}}{(1 + \gamma)^{m_{1+}+m_{2+}}} U^{m_{10}+m_{20}}(1 - U)^{m_{00}} V^{m_{11}+m_{21}}(1 - V)^{m_{01}}.$$

This parametrization splits the likelihood function into three unrelated pieces, each piece related to a single parameter. This makes it very easy to derive Jeffreys' prior. The first and second derivatives of the log-likelihood function with respect to γ, U, and V are

$$\frac{\partial l(\gamma)}{\partial \gamma} = \frac{m_{1+}}{\gamma} - \frac{m_{2+}}{1 - \gamma} - \frac{m_{1+} + m_{2+}}{1 + \gamma}, \frac{\partial^2 l(\gamma)}{\partial \gamma^2} = -\frac{m_{1+}}{\gamma^2} - \frac{m_{2+}}{(1 - \gamma)^2} + \frac{m_{1+} + m_{2+}}{(1 + \gamma)^2},$$

$$\frac{\partial l(U)}{\partial U} = \frac{(m_{20} + m_{10})}{U} - \frac{m_{00}}{1 - U}, \frac{\partial^2 l(U)}{\partial U^2} = -\frac{(m_{20} + m_{10})}{U^2} - \frac{m_{00}}{(1 - U)^2},$$

$$\frac{\partial l(V)}{\partial V} = \frac{(m_{21} + m_{11})}{V} - \frac{m_{01}}{1 - V}, \frac{\partial^2 l(V)}{\partial V^2} = -\frac{(m_{21} + m_{11})}{V^2} - \frac{m_{01}}{(1 - V)^2}.$$

Let $r = \dfrac{m_{+1}}{m_{+0}}$ be the ratio of the sample size in the two groups. Thus, we have

$$E\Big[-\frac{\partial^2 l(\gamma)}{\partial \gamma^2}\Big] = \frac{2m_{+0}(U + rV)}{\gamma(1 - \gamma)(1 + \gamma)^2}, \quad E\Big[-\frac{\partial^2 l(U)}{\partial U^2}\Big] = \frac{m_{+0}}{U(1 - U)},$$

$$E\Big[-\frac{\partial^2 l(V)}{\partial V^2}\Big] = \frac{m_{+1}}{V(1 - V)}.$$

Hence, Jeffreys' prior under the parameterization (γ, U, V) is

$$\pi_J(\gamma, u, v) \propto \sqrt{\frac{(u + rv)}{\gamma(1 - \gamma)(1 + \gamma)^2 u(1 - u)v(1 - v)}}, \qquad 0 < \gamma, u, v < 1,$$

and it is proper. Theorem A.1 implies that Jeffreys' prior density in the parameterization $(\gamma, \lambda_0, \lambda_1)$ is

$$\pi_J(\gamma, \lambda_0, \lambda_1) \propto \sqrt{\frac{(1 + \gamma)(\lambda_0 + r\lambda_1)}{\gamma(1 - \gamma)\lambda_0\lambda_1 \big[1 - (1 + \gamma)\lambda_0\big] \big[1 - (1 + \gamma)\lambda_1\big]}},$$

where $(\gamma, \lambda_0, \lambda_1) \in \Omega$. $\qquad\qquad\square$

Appendix 2: Derivation of Reference Priors

Proof. We first derive the joint reference prior for the parameterization (γ, U, V) and then transform back to derive the joint reference prior for $(\gamma, \lambda_0, \lambda_1)$. See Yang (1995) for justification. We also adopt the notation in Yang (1995).

Case 1: Consider the group ordering $\{U, V\}$ and then γ or $\{V, U\}$ and then γ. We have $h_1 = \dfrac{m_{+0}}{u(1 - u)}$, $h_2 = \dfrac{m_{+1}}{v(1 - v)}$, and $h_3 = \dfrac{2m_{+0}(u + rv)}{\gamma(1 - \gamma)(1 + \gamma)^2}$. Thus, we obtain

$$\pi_R^1(u, v, \gamma) = \frac{|h_3|^{1/2}}{\int |h_3|^{1/2}d\gamma} \frac{\exp\left\{\frac{1}{2} \int \log(h_1 h_2)\, d\gamma\right\}}{\exp\left\{\frac{1}{2} \iiint \log(h_1 h_2) d\gamma du dv\right\}},$$

$$\propto \frac{\sqrt{2}}{\pi} \frac{\gamma^{1/2-1}(1 - \gamma)^{1/2-1}}{(1 + \gamma)} \frac{u^{1/2-1}(1 - u)^{1/2-1}}{\mathbf{B}(1/2, 1/2)} \frac{v^{1/2-1}(1 - v)^{1/2-1}}{\mathbf{B}(1/2, 1/2)},$$

and

$$\pi_R^1(\gamma, \lambda_0, \lambda_1)$$
$$= \frac{\sqrt{2}}{\pi} \gamma^{1/2-1}(1 - \gamma)^{1/2-1} \frac{\lambda_0^{1/2-1}\big[1 - (1 + \gamma)\lambda_0\big]^{1/2-1}}{\mathbf{B}(1/2, 1/2)} \frac{\lambda_1^{1/2-1}\big[1 - (1 + \gamma)\lambda_1\big]^{1/2-1}}{\mathbf{B}(1/2, 1/2)}.$$

Case 2: Consider the group ordering of $\{\gamma\}$ and then $\{U, V\}$ or the ordering $\{\gamma\}$ and then $\{V, U\}$. We have $h_1 = \dfrac{2m_{+0}(u + rv)}{\gamma(1 - \gamma)(1 + \gamma)^2}$, $h_2 = \dfrac{m_{+0}}{u(1 - u)}$, $h_3 = \dfrac{m_{+1}}{v(1 - v)}$. Thus, the reverse reference prior is

$$\pi_R^2(u, v, \gamma) = \frac{|h_1 h_2|^{1/2}}{\int |h_1 h_2|^{1/2}du dv} \frac{\exp\left\{\frac{1}{2} \iint \log(h_3)\, du\, dv\right\}}{\exp\left\{\frac{1}{2} \iiint \log(h_3) du dv d\gamma\right\}}$$
$$= \frac{u^{1/2-1}(1 - u)^{1/2-1}}{\mathbf{B}(1/2, 1/2)} \frac{v^{1/2-1}(1 - v)^{1/2-1}}{\mathbf{B}(1/2, 1/2)} \frac{\sqrt{2}}{\pi} \frac{\gamma^{1/2-1}(1 - \gamma)^{1/2-1}}{(1 + \gamma)}$$
$$= \pi_R^1(u, v, \gamma).$$

Case 3: Here one starts with some subjective joint prior distribution for the parameters for which one has a good knowledge of and for the other parameters, one uses a non-informative prior distribution to reflect the lack of knowledge. Assume there is prior evidence for assuming the following conditional joint distribution

$$\pi_B^3(\lambda_0, \lambda_1 | \gamma) = \frac{\lambda_0^{a_0-1} \left(\frac{1}{1+\gamma} - \lambda_0\right)^{b_0-1}}{\left(\frac{1}{1+\gamma}\right)^{a_0+b_0-1} \mathbf{B}(a_0, b_0)} \frac{\lambda_1^{a_1-1} \left(\frac{1}{1+\gamma} - \lambda_1\right)^{b_1-1}}{\left(\frac{1}{1+\gamma}\right)^{a_1+b_1-1} \mathbf{B}(a_1, b_1)}, \quad 0 < \lambda_0, \lambda_1 < \frac{1}{1+\gamma}.$$

about λ_0 and λ_1 given γ. That is,

$$\lambda_0 | \gamma \sim \mathbf{Be}\left(a_0, b_0; 0, \frac{1}{1+\gamma}\right), \ \lambda_1 | \gamma \sim \mathbf{Be}\left(a_1, b_1; 0, \frac{1}{1+\gamma}\right)$$

and both λ_0 and λ_1 are conditionally independent given γ. But one has no idea about a prior for γ. A solution to this problem is to use a reference prior for γ. Under our partial prior specification, the reference prior is Jeffreys' prior associated to the integrated likelihood (integrating out U and V),

$$L(\gamma) \propto \frac{\gamma^{m_{1+}}(1-\gamma)^{m_{2+}}}{(1+\gamma)^{m_{1+}+m_{2+}}}.$$

Hence, the reference prior corresponding to this integrated likelihood is

$$\pi_R^3(\gamma) \propto \sqrt{\frac{m_{+0}E(\lambda_0) + m_{+1}E(\lambda_1)}{\gamma(1-\gamma)(1+\gamma)^2}} \propto \sqrt{\frac{1}{\gamma(1-\gamma)(1+\gamma)^2}},$$

and it is proper. Thus, the joint prior distribution over Ω is then

$$\pi_R^3(\gamma, \lambda_0, \lambda_1)$$

$$= \frac{\sqrt{2}}{\pi} \frac{\gamma^{1/2-1}(1-\gamma)^{1/2-1}}{(1+\gamma)} \frac{\lambda_0^{a_0-1} \left(\frac{1}{1+\gamma} - \lambda_0\right)^{b_0-1}}{\left(\frac{1}{1+\gamma}\right)^{a_0+b_0-1} \mathbf{B}(a_0, b_0)} \frac{\lambda_1^{a_1-1} \left(\frac{1}{1+\gamma} - \lambda_1\right)^{b_1-1}}{\left(\frac{1}{1+\gamma}\right)^{a_1+b_1-1} \mathbf{B}(a_1, b_1)},$$

and it belongs to the family of prior distributions discussed in (12).

Case 4: Similarly, in the second setup of partial prior specification, one assumes that there is available a family of prior distributions for γ, for example,

$$\pi_B^4(\gamma) = \frac{2^\mu}{\mathbf{B}(\mu, \nu)} \frac{\gamma^{\mu-1}(1-\gamma)^{\nu-1}}{(1+\gamma)^{\mu+\nu}},$$

and one would like to find the joint reference prior distribution for the pair (λ_0, λ_1) conditional on γ. The proposed reference prior under this partial prior specification is

$$\pi_R^4(\lambda_0, \lambda_1 | \gamma) \propto \left| \det(S) \right|^{1/2} = \sqrt{F_{22}F_{33}} \propto \frac{(1+\gamma)}{\sqrt{\lambda_0 \lambda_1 \left[1 - (1+\gamma)\lambda_0\right] \left[1 - (1+\gamma)\lambda_1\right]}},$$

where S is the lower 2×2 left corner matrix of the Fisher information matrix. Hence, the joint prior distribution of $(\gamma, \lambda_0, \lambda_1)$ over Ω is

$$\pi_R^4(\gamma, \lambda_0, \lambda_1)$$
$$= \frac{2^\mu}{\mathbf{B}(\mu,\nu)} \frac{\gamma^{\mu-1}(1-\gamma)^{\nu-1}}{(1+\gamma)^{\mu+\nu-1}} \frac{\lambda_0^{1/2-1}[1-(1+\gamma)\lambda_0]^{1/2-1}}{\mathbf{B}(1/2,1/2)} \frac{\lambda_1^{1/2-1}[1-(1+\gamma)\lambda_1]^{1/2-1}}{\mathbf{B}(1/2,1/2)}$$

and it belongs again to the family of prior distributions discussed in (12). $\square$

Appendix 3: Results for Posterior Calculation

Proposition A.1. *Let γ have density $f(\gamma) = \dfrac{2^\mu}{\mathbf{B}(\mu,\nu)} \dfrac{\gamma^{\mu-1}(1-\gamma)^{\nu-1}}{(1+\gamma)^{\mu+\nu}}$, $0 < \gamma < 1$.*
Then, the density of $\phi = logit(\gamma) + \log(2)$ is $f(\phi) = \dfrac{1}{\mathbf{B}(\mu,\nu)} \dfrac{e^{\mu\phi}}{\left(1+e^\phi\right)^{\mu+\nu}}$, which is well known to be the density of $logit(p)$, where $p \sim \mathbf{Be}(\mu,\nu)$.

Proof. $\gamma = \dfrac{e^{\phi-\log(2)}}{1+e^{\phi-\log(2)}}$. We have $1-\gamma = \dfrac{1}{1+e^{\phi-\log(2)}}$, $1+\gamma = \dfrac{1+2e^{\phi-\log(2)}}{1+e^{\phi-\log(2)}}$, and $\dfrac{d\gamma}{d\phi} = \dfrac{e^{\phi-\log(2)}}{(1+e^{\phi-\log(2)})^2}$. Thus, we obtain

$$f(\phi) = \frac{2^\mu}{\mathbf{B}(\mu,\nu)} \frac{e^{(\mu-1)(\phi-\log(2))}}{(1+e^{\phi-\log(2)})^{\mu-1}} \frac{1}{(1+e^{\phi-\log(2)})^{\nu-1}} \frac{(1+e^{\phi-\log(2)})^{\mu+\nu}}{(1+2e^{\phi-\log(2)})^{\mu+\nu}} \frac{e^{\phi-\log(2)}}{(1+e^{\phi-\log(2)})^2}$$
$$= \frac{2^\mu}{\mathbf{B}(\mu,\nu)} \frac{e^{\mu(\phi-\log(2))}}{(1+2e^{\phi-\log(2)})^{\mu+\nu}} = \frac{1}{\mathbf{B}(\mu,\nu)} \frac{e^{\mu\phi}}{(1+e^\phi)^{\mu+\nu}}. \qquad \square$$

Proposition A.2. *Let γ have density $f(\gamma) = \dfrac{2^\mu}{\mathbf{B}(\mu,\nu)} \dfrac{\gamma^{\mu-1}(1-\gamma)^{\nu-1}}{(1+\gamma)^{\mu+\nu}}$, $0 < \gamma < 1$.*
Then, $\pi = \dfrac{1-\gamma}{1+\gamma} \sim \mathbf{Be}(\nu,\mu)$.

Proof. We have $\gamma = \dfrac{1-\pi}{1+\pi}$. So $1-\gamma = \dfrac{2\pi}{1+\pi}$, $1+\gamma = \dfrac{2}{1+\pi}$, and $\dfrac{d\gamma}{d\pi} = \dfrac{-2}{(1+\pi)^2}$. Thus, we have

$$f(\pi) = \frac{2^\mu}{\mathbf{B}(\mu,\nu)} \frac{(1-\pi)^{\mu-1}}{(1+\pi)^{\mu-1}} \frac{2^{\nu-1}\pi^{\nu-1}}{(1+\pi)^{\nu-1}} \frac{(1+\pi)^{\mu+\nu}}{2^{\mu+\nu}} \frac{2}{(1+\pi)^2} = \frac{1}{\mathbf{B}(\nu,\mu)} \pi^{\nu-1}(1-\pi)^{\mu-1}.$$
$$\square$$

The marginal prior distribution $\pi(\gamma)$ has the following properties. When $\mu = \nu = 1$, $\pi(\gamma)$ is decreasing. When $\mu = 1$ and $\nu < 1$, $\pi(\gamma)$ is U-shaped, the anti-mode being at ν. When $\mu = 1$ and $\nu > 1$ or $\nu = 1$ and $\mu < 1$ or $\mu > 1$ and $\nu < 1$, $\pi(\gamma)$ is decreasing.

When $\nu = 1$ and $1 < \mu < 3$, $\pi(\gamma)$ is unimodal and the mode is at $\gamma = \dfrac{\mu - 1}{2}$. When $\nu = 1$ and $\mu \geq 3$, it is J-shaped. When $\mu, \nu > 1$, $\pi(\gamma)$ is unimodal and the mode is at $\gamma = \dfrac{2(\mu - 1)}{2\nu + \mu - 1 + \sqrt{\Lambda}}$, where $\Lambda = (2\nu + \mu - 1)^2 - 8(\mu - 1)$. When $\mu < 1$ and $\nu < 1$, $\pi(\gamma)$ is U-shaped, and the anti-mode is at $\gamma = \dfrac{2\nu + \mu - 1 + \sqrt{\Lambda}}{4}$.

Appendix 4: Posterior Distribution of Δ and R

To derive the posterior distribution of Δ and R, we consider the parameterization (γ, U, V). Under this parameterization, the posterior distributions of interest belong to the family

$$
\pi(\gamma, u, v \,|\, D) = \frac{1}{K} \frac{2^{m_{1+}+\alpha}}{\mathbf{B}(m_{1+} + \alpha, m_{2+} + \beta)} \frac{\gamma^{m_{1+}+\alpha-1}(1-\gamma)^{m_{2+}+\beta-1}}{(1+\gamma)^{m_{1+}+m_{2+}+\alpha+\beta}} (u + rv)^d
$$
$$
\times \frac{u^{m_{10}+m_{20}+a_0-1}(1-u)^{m_{00}+b_0-1}}{\mathbf{B}(m_{10} + m_{20} + a_0, m_{00} + b_0)} \frac{v^{m_{11}+m_{21}+a_1-1}(1-v)^{m_{01}+b_1-1}}{\mathbf{B}(m_{11} + m_{21} + a_1, m_{01} + b_1)},
$$

where $0 < \gamma, u, v < 1$ and K is the normalizing constant. The choice $d = 1/2, a_0 = b_0 = a_1 = b_1 = 1/2$ corresponds to Jeffreys' posterior distribution and the choice $d = 0, a_0 = b_0 = a_1 = b_1 = 1/2$ corresponds to Bernardo's posterior distribution.

Proposition A.3. *The posterior distribution of the risk difference, $\Delta = \lambda_1 - \lambda_0 = \dfrac{V - U}{1 + \gamma}$, has the complex integral form*

$$
\pi(\Delta \,|\, D)
$$
$$
= \frac{1}{K} \int_{-\frac{1+|\Delta|}{|\Delta|}}^{\frac{1-|\Delta|}{|\Delta|}} \frac{2^{m_{1+}+\alpha}}{\mathbf{B}(m_{1+} + \alpha, m_{2+} + \beta)} \frac{\gamma^{m_{1+}+\alpha-1}(1-\gamma)^{m_{2+}+\beta-1}}{(1+\gamma)^{m_{1+}+m_{2+}+\alpha+\beta}}
$$
$$
\times \int_{\max(0, -(1+\gamma)\Delta)}^{\min(1, 1-(1+\gamma)\Delta)} \left((1+r)u + r(1+\gamma)\Delta \right)^d \frac{u^{m_{10}+m_{20}+a_0-1}(1-u)^{m_{00}+b_0-1}}{\mathbf{B}(m_{10} + m_{20} + a_0, m_{00} + b_0)}
$$
$$
\times \frac{\left(u + (1+\gamma)\Delta \right)^{m_{11}+m_{21}+a_1-1} \left(1 - u - (1+\gamma)\Delta \right)^{m_{01}+b_1-1}}{\mathbf{B}(m_{11} + m_{21} + a_1, m_{01} + b_1)} \, du \, d\gamma.
$$

We also have

$$
P(\lambda_1 - \lambda_0 > \Delta_0 | D)
$$
$$
= \frac{2^{m_{1+}+\frac{1}{2}}}{\mathbf{B}(m_{1+} + \frac{1}{2}, m_{2+} + \frac{1}{2})} \int_0^1 \int_0^1 \int_{v > u + \Delta_0/(1+\gamma)}^1 \frac{\gamma^{m_{1+}+\frac{1}{2}-1}(1-\gamma)^{m_{2+}+\frac{1}{2}-1}}{(1+\gamma)^{m_{1+}+m_{2+}+1}}
$$
$$
\times \frac{(u + rv)^d}{K} \frac{u^{m_{10}+m_{20}+\frac{1}{2}-1}(1-u)^{m_{00}+\frac{1}{2}-1}}{\mathbf{B}(m_{10} + m_{20} + \frac{1}{2}, m_{00} + \frac{1}{2})} \frac{v^{m_{11}+m_{21}+\frac{1}{2}-1}(1-v)^{m_{01}+\frac{1}{2}-1}}{\mathbf{B}(m_{11} + m_{21} + \frac{1}{2}, m_{01} + \frac{1}{2})} dv \, du \, d\gamma.
$$

When $\Delta_0 = 0$, this expression depends no longer on γ and when $d = 0$ it is even simpler.

Proposition A.4. *The posterior distribution of the risk ratio, $R = \dfrac{\lambda_1}{\lambda_0} = \dfrac{V}{U}$, does not depend on γ and it has the simpler integral form*

$$
\pi(R \mid D) = \begin{cases}
\dfrac{R^{m_{11}+m_{21}+a_1-1}(1+rR)^d}{K\,K^*} \displaystyle\int_0^1 u^{m_{1+}+m_{2+}+d+a_0+a_1-1}(1-u)^{m_{00}+b_0-1} \\
\qquad\qquad\qquad \times (1-Ru)^{m_{01}+b_1-1}\, du\,, \qquad 0 < R \le 1, \\[2ex]
\dfrac{R^{-(m_{10}+m_{20}+a_1+d+1)}(1+rR)^d}{K\,K^*} \displaystyle\int_0^1 v^{m_{1+}+m_{2+}+d+a_0+a_1-1}(1-v)^{m_{01}+b_1-1} \\
\qquad\qquad\qquad \times (1-Rv)^{m_{00}+b_0-1}\, dv\,, \qquad R > 1,
\end{cases}
$$

where $K^* = \mathbf{B}(m_{10}+m_{20}+a_0, m_{00}+b_0)\mathbf{B}(m_{11}+m_{21}+a_1, m_{01}+b_1)$. When $d = 0$, it can be shown that $\pi(R \mid D)$ is unimodal when m_{00} and m_{01} are positive. We also have

$$
P(R > R_0 \mid D) = \int_0^1 \int_{v>R_0 u} \left[\frac{(u+rv)^d}{K} \frac{u^{m_{10}+m_{20}+\frac{1}{2}-1}(1-u)^{m_{00}+\frac{1}{2}-1}}{\mathbf{B}\left(m_{10}+m_{20}+\frac{1}{2}, m_{00}+\frac{1}{2}\right)} \right.
$$
$$
\left. \times \frac{v^{m_{11}+m_{21}+\frac{1}{2}-1}(1-v)^{m_{01}+\frac{1}{2}-1}}{\mathbf{B}\left(m_{11}+m_{21}+\frac{1}{2}, m_{01}+\frac{1}{2}\right)} \right] dv\,du.
$$