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RESEARCH ARTICLE

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A Bayesian re-analysis of the DANFLU-1 trial

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ABSTRACT

DANFLU-1 was an open-label, pragmatic feasibility trial which randomized persons aged 65 to 79 years to high-dose inactivated influenza vaccine (HD-IIV) or standard-dose inactivated influenza vaccine (SD-IIV). The trial found that HDIV was associated with a reduced incidence of death and hospitalization for influenza or pneumonia as compared to SDIV. Bayesian analysis offers a framework for probabilistic interpretation of trial data and provides a method for incorporating prior information into the analysis. This study presents a post-hoc, Bayesian re-analysis of the DANFLU-1 trial. We conducted a Bayesian re-analysis of the DANFLU-1 trial, which randomly assigned 12,477 adults (65–79 years) 1:1 to HDIV or SDIV during the 2021/2022 season. The trial used Danish nationwide registers for data collection including baseline and follow-up data. This re-analysis applied neutral non-informative, evidence-based, and neutral skeptical priors. The evidence-based priors were informed solely by randomized trials published before DANFLU-1. Relative vaccine effectiveness (rVE) with 95% credible intervals (CrI), and posterior probabilities were estimated using Bayesian log-binomial regression models. Probabilities of rVE >0%, 10% and 20% were estimated. The findings were consistent across different priors. There was a greater than 95% probability of any benefit (i.e. rVE >0%) for all-cause mortality and hospitalization due to pneumonia/influenza, regardless of the prior used. For pneumonia/influenza hospitalization, the probabilities of rVE >10% were at least 95% with the non-informative and evidence-based priors, while it was 93.2% with the skeptical prior. For all-cause mortality, the probabilities of rVE > 10% ranged from 91.1% to 98.4% across priors. For the remaining outcomes, including cardiorespiratory hospitalization and any hospitalization, the probabilities of of rVE >10% ranged from 25.0% to 59.0% across priors. This Bayesian re-analysis of DANFLU-1 demonstrated robust results, with high probabilities of any benefit (rVE >0%) for all-cause mortality and hospitalization due to pneumonia/influenza. We also found high probabilities of an rVE > 10% for both outcomes, indicating robust findings supportive of clinical benefit. As a feasibility trial, the findings warrant further Bayesian investigation of adequately powered trials.

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Introduction

Older adults are at increased risk of developing severe outcomes following influenza infection, including hospitalization and death.[1] As a result, annual influenza vaccination is widely recommended for all individuals aged 65 years and older.[1,2] However, multiple studies have shown that immune responses to

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standard-dose influenza vaccines (SDIV) are often diminished in older adults compared to younger individuals.[3] The high-dose influenza vaccine (HDIV) has been developed to address this issue, and has been shown to elicit stronger immune responses and offer superior protection against influenza infection compared to SDIV.[4,5] Additionally, evidence suggests that HDIV may reduce the risk of severe outcomes, including hospitalization and mortality, relative to SDIV.[6,7] We recently conducted the DANFLU-1 feasibility trial (Feasibility of Randomizing Danish Citizens Aged 65–79 Years to High-Dose Quadrivalent Influenza Vaccine vs. Standard-Dose Quadrivalent Influenza Vaccine in a Pragmatic Registry-Based Setting) randomizing 12,477 participants 1:1 to HDIV or SDIV. Although the trial was not powered for clinical outcomes, in frequentist analyses, the HDIV group showed a lower incidence of hospitalization for influenza or pneumonia (relative vaccine effectiveness (rVE), 64.4%; 95% confidence interval (CI), 24.4 to 84.6) and a lower incidence of all-cause death (rVE, 48.9%; 95% CI, 11.5 to 71.3) when compared to the SDIV group. In this report, we present a Bayesian re-analysis of the DANFLU-1 trial to provide a more nuanced, probabilistic interpretation of the findings. By incorporating prior knowledge from the broader evidence base on high-dose influenza vaccination, this analysis complements the original frequentist results and enhances the clinical and public health interpretability of the trial's outcomes.

Methods

DANFLU-1 study design

The design and conduct of the DANFLU-1 trial have been described in detail elsewhere.[6] In brief, DANFLU-1 was a randomized, open-label, pragmatic, controlled trial assessing the feasibility of allocating individuals aged 65 to 79 years to receive either HDIV or SDIV in a 1:1 ratio. The trial was conducted during the 2021–2022 influenza season and enrolled 12,477 participants. The only exclusion criterion was allergy to the study vaccines. Recruitment and vaccination were carried out by a private provider operating within the framework of the Danish national influenza vaccination program. The study was centrally organized, with oversight of safety and data processes. Data on baseline characteristics, follow-up, and outcomes were primarily obtained through linkage with Danish nationwide health registers. Participants were enrolled between October and November 2021, and follow-up continued through May 31, 2022. All necessary approvals for trial conduct and data linkage were obtained. For further details, including regulatory approvals and ethical considerations, please refer to the primary publication describing the main trial results.[6] Due to the register-based nature of the trial, baseline and follow-up data were available for 99.9% of participants. Accordingly, complete case analysis was applied.

The study was approved by the Regional Committee on Health Research Ethics in Denmark (H-21035316) and the Danish Medicines Agency (EudraCT no. 2021-003,170-31). It was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The full study protocol and statistical analysis plan are available with the main DANFLU-1 trial publication.[6] The trial was registered at ClinicalTrials.gov (NCT05048589).

Bayesian inference

Bayesian methods offer a flexible and transparent approach to interpreting clinical trial data.[8,9] Unlike traditional frequentist approaches, which focus on rejecting a null hypothesis, Bayesian analyses provide direct estimates of the probabilities that a treatment is beneficial or harmful, and whether treatment effects exceed clinically meaningful thresholds. This is achieved by combining prior information – such as expert opinion or external evidence, or simply no prior information – with the observed trial data to generate a posterior probability distribution.[10] Minimally informative or non-informative priors are also commonly used to allow the data to drive inference. This framework not only supports a nuanced interpretation of treatment effects but also facilitates clinical decision-making by quantifying the probability of achieving specific outcome thresholds. For further details on the benefits of Bayesian analysis, we refer to other sources.[9,11]

Bayesian re-analysis

The primary objective of the DANFLU-1 trial was to assess feasibility.[6] However, several clinical outcomes were also evaluated, including all-cause mortality, hospitalization for influenza or pneumonia, hospitalization for respiratory disease, hospitalization for cardiorespiratory disease, and hospitalization for any cause. These outcomes formed the focus of the present Bayesian re-analysis. Although DANFLU-1 was initially analyzed with a frequentist approach, data from randomized clinical trials are well suited for Bayesian analysis which offers an intuitive and flexible approach to the analysis and interpretation of clinical trial data.[10] The results of the Bayesian analysis are reported in accordance with the ROBUST guidelines.[12] For each outcome, we estimated posterior relative vaccine effectiveness (rVE) with 95% credible intervals and calculated the posterior probability that rVE exceeded a range of thresholds, from rVE of >0%, >10% and >20%, with rVE >10% as the primary reported threshold. We used a range of priors to evaluate the robustness of our findings, including a non-informative prior, an evidence-based prior, and a neutral skeptical prior. All priors were normally distributed on the log-relative risk scale. The non-informative prior was specified as a normal distribution centered at a relative vaccine effectiveness (rVE) of 0 (equivalent to a relative risk of 1) with a standard deviation of 100 on the log-relative risk scale. This very wide prior is used to ensure that posterior estimates are driven almost entirely by the observed data, with negligible influence from prior assumptions. The non-informative prior was centered at rVE = 0 (equivalent to a relative risk of 1) with a standard deviation of 100 on the log-relative risk scale. This specification exerts minimal influence on the posterior estimates, allowing the observed data to dominate inference. The evidence-based priors were derived from a systematic review with meta-analysis of randomized controlled trials published prior to the conduct of DANFLU-1, ensuring that only contemporaneously available data informed the prior specification.[11] In brief, the meta-analysis included up to 97,126 participants from 4 trials and the main estimates were derived using random-effects models. Prior means and standard deviations (on the log-relative risk scale), and corresponding estimates of relative vaccine effectiveness (rVE) from prior trials are summarized in Table 1. The skeptical prior was neutral and thus also centered at 0 but had a standard deviation of 0.0822 on the log relative risk scale, assuming a 10% probability of rVE ≥10%. All priors used in the analysis are displayed on a common scale in Figure 1 and are available for inspection. All statistical analyses used the original intention-to-treat trial population. In all models, the prior for the intercept was specified as a non-informative normal distribution with mean 0 and standard deviation 100. Calculations were made with Stata 18/MP. Relative risk estimates were derived using unadjusted Bayesian log-binomial regression models and used to calculate rVE estimates. We assessed model convergence using multiple diagnostics. For all estimated parameters, we visually inspected trace plots and posterior density plots. Convergence was further evaluated using the potential scale reduction factor ($\widehat{R}$), with a threshold of ≤1.01 indicating acceptable convergence. We also ensured that the effective sample size (ESS) was sufficient, with all parameters having an ESS >1000. Density plots of the full posterior

Table 1. Priors used in the study, including evidence-based priors informed by meta-analyses of randomized clinical trials available at the time of DANFLU-1 initiation, as well as the non-informative and skeptical priors, are summarized below.

Outcome	Number of trials	Number of total participants	Meta analysis model	Estimate from previous trials rVE (95% CI)	Prior mean, standard deviation log RR
All-cause death	3	87954	Random effects	rVE 4.9% (−6.5%; 15.1%)	−0.0502, 0.0581
P/I hospitalization	3	94169	Random effects	rVE 27.3% (15.3%; 37.6%)	−0.3188, 0.0779
CR hospitalization	1	31989	Random effects	rVE 18.2% (6.8%; 28.1%)	−0.2009, 0.0666
Any hospitalization	3	87954	Random effects	rVE 11.9% (2.0%; 20.7%)	−0.1267, 0.1080
Non-informative	NA	NA	NA	NA	0, 100
Skeptical	NA	NA	NA	NA	0, 0.0822

Evidence-based estimates from "J. K. H. Lee et al., "Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis," Expert Rev. Vaccines, vol. 17, no. 5, pp. 435–443, May 2018, doi: 10.1080/14760584.2018.1471989." rVE, relative vaccine effectiveness. The non-informative prior reflects minimal prior assumptions, specified as a normal distribution centered at rVE = 0 with a standard deviation of 100 on the log-relative risk scale. The skeptical prior is also centered at rVE = 0 but with a standard deviation of 0.0822, corresponding to a 10% prior probability that the vaccine reduces the risk of events by 10% or more.

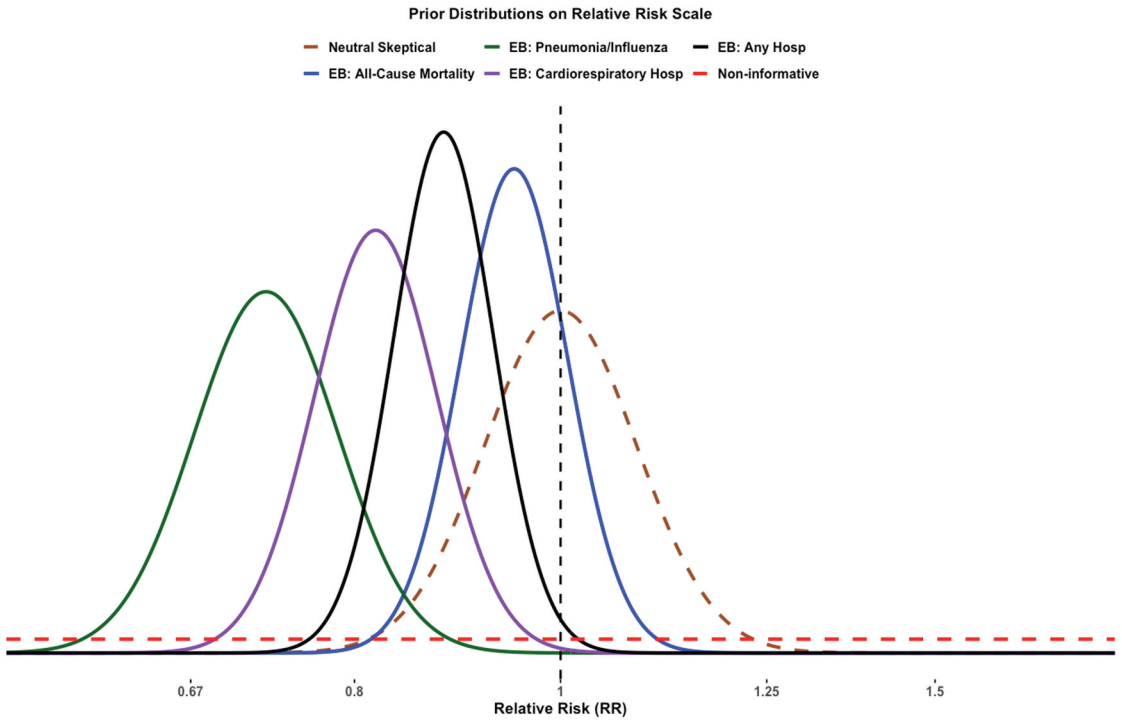

Figure 1. Prior distributions used in the analysis. Figure showing the priors used in the analysis. The x-axis shows the effect size on the relative risk scale. Relative risk is related to relative vaccine effectiveness (rVE) through rVE = (1-RR)*100%. EB; evidence-based, Any Hosp; any hospitalization, CR Hosp; cardiorespiratory hospitalization, P/I; hospitalization for pneumonia or influenza.

rVE distributions for all outcomes and accompanying prior specifications are displayed in Figure 2. There were no issues with non-convergence. Posterior distributions were approximated using 10,000 Monte Carlo samples drawn from the posterior via Markov Chain Monte Carlo (MCMC) simulation. Credible intervals were computed as equal-tailed, quantile-based 95% intervals from the posterior distribution.

Results

The Bayesian re-analysis produced consistent findings across all three priors for the outcomes of all-cause mortality and hospitalization for P/I. For these two outcomes, there were high probabilities (>90%) of benefit (rVE >0% and rVE >10%) under all prior assumptions used (Table 2 and Figure 2).

For hospitalization due to P/I, the posterior median rVE was highest with the non-informative prior (rVE 65.2%) and remained considerable under the evidence-based (44.9%) and skeptical (34.6%) priors. The probabilities of any benefit (i.e. rVE >0%) exceeded 97% for all priors, and the probabilities of rVE >10% exceeded 93%. The probabilities of rVE >20% ranged from 82.4% to 99.4% (Table 2 and Figure 2).

With respect to hospitalization for cardiorespiratory disease, the posterior median rVE ranged from 9.8% (skeptical prior) to 13.3% (evidence-based prior). The probabilities of any benefit ranged from 79.9% to 88.8% while the probabilities of reaching rVE >10% ranged from 48.7% to 62.2% (Table 2 and Figure 2).

For all-cause hospitalization, the posterior median rVE was relatively low across all priors (6.5% to 7.4%). While the probabilities of any benefit remained above 87%, the probabilities of achieving rVE >10% were 25.0% to 31.7%, and the probabilities of an rVE >20% were ≤0.5% (Table 2 and Figure 2).

For all-cause mortality, the posterior medians rVE for all-cause mortality ranged from 29.8% to 49.7% across priors. The probabilities of any benefit (rVE >0%) were ≥97.4% for all priors, while the probabilities of achieving rVE >10% ranged from 90.2% (evidence-based prior) to 98.4% (non-informative prior). The probabilities of an rVE >20% ranged from 72.5% to 95.6% (Table 2 and Figure 2).

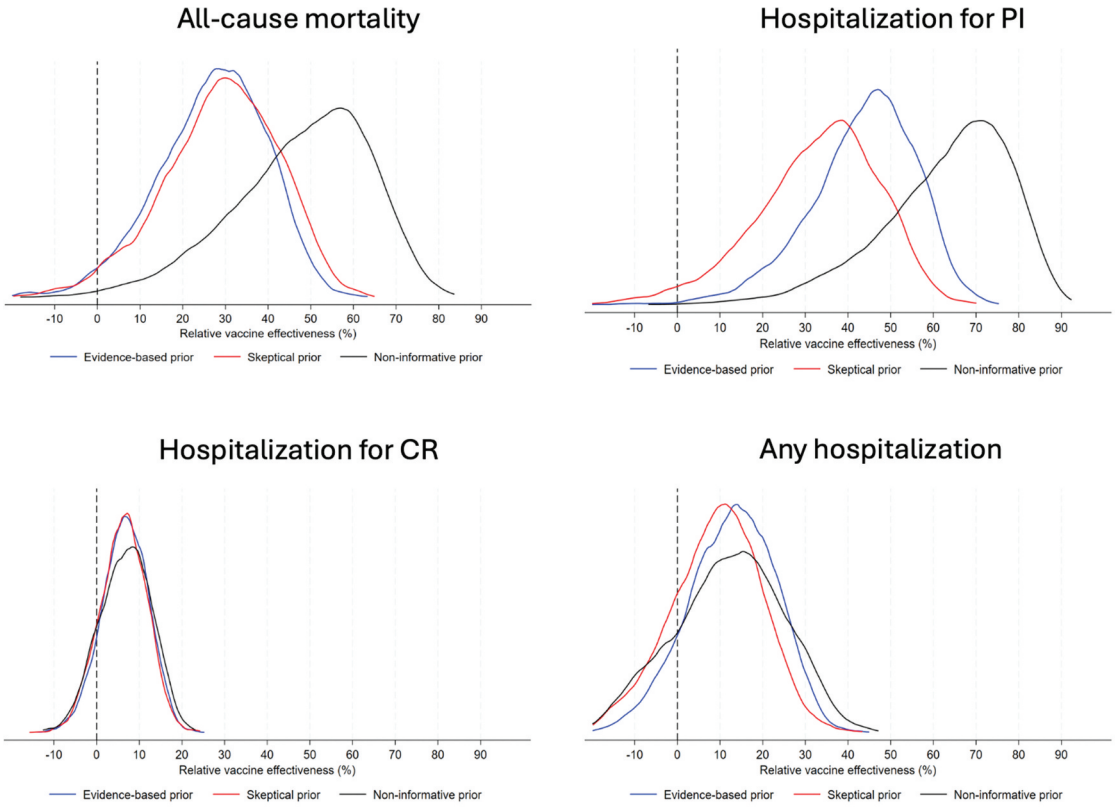

Figure 2. Posterior distributions of relative vaccine effectiveness (rVE) across prior specifications and clinical outcomes. Posterior distributions of rVE for high-dose influenza vaccine versus standard-dose, estimated using Bayesian models under three different prior specifications: non-informative priors (black), neutral skeptical priors (red), and evidence-based priors (blue). Vertical dashed lines indicate the threshold for no difference (rVE = 0%). Distributions are shown for four out-comes: all-cause mortality, hospitalization for pneumonia or influenza (P/I), hospitalization for cardiorespiratory (CR) causes, and all-cause hospitalization.

Table 2. Bayesian posterior estimates of relative vaccine effectiveness (rVE) and probabilities of rVE thresholds by outcome and prior.

Outcome and prior	Posterior median rVE [95% CrI]	Probability of rVE >0%	Probability of rVE >10%	Probability of rVE >20%
Hospitalization for pneumonia/influenza (P/I)				
Non informative prior	65.2% [31.3%; 83.9%]	99.9%	99.9%	99.4%
Evidence-based prior	44.9% [15.5%; 63.3%]	99.8%	98.7%	95.3%
Neutral Skeptical prior	34.6% [−0.3%; 56.4%]	97.4%	93.2%	82.4%
Hospitalization for cardiorespiratory (CR) disease				
Non informative prior	12.5% [−13.2%; 33.2%]	84.4%	59.0%	22.4%
Evidence-based prior	13.3% [−8.5%; 30.9%]	88.8%	62.2%	25.3%
Neutral Skeptical prior	9.8% [−14.0%; 27.8%]	79.9%	48.7%	14.7%
Hospitalization any cause				
Non informative prior	7.0% [−4.0%; 16.8%]	88.3%	29.1%	0%
Evidence-based prior	7.4% [−3.4%; 17.1%]	90.9%	31.7%	0.5%
Neutral Skeptical prior	6.5% [−4.8%; 16.3%]	87.0%	25.0%	0.5%
All-cause mortality				
Non informative prior	49.7% [14.0%; 71.1%]	99.6%	98.4%	95.6%
Evidence-based prior	28% [0.0%; 48.0%]	97.4%	90.2%	72.5%
Neutral Skeptical prior	29.8% [−0.3%; 52.1%]	97.4%	91.1%	75.9%

rVE, relative vaccine effectiveness; CrI, credible interval.

Discussion

The original frequentist analysis of the DANFLU-1 trial found that HDIV reduced the risk of hospitalization for P/I, with an estimated rVE of 64.4% (95% CI, 24.4% to 84.6%) and reduced the risk of all-cause mortality, with an rVE of 48.9% (95% CI, 11.5% to 71.3%).[6] In this Bayesian re-analysis, we leveraged the

strengths of Bayesian methods to estimate the probabilities of treatment effects exceeding clinically relevant thresholds. We applied a range of prior distributions, including non-informative priors, skeptical priors, and evidence-based priors informed by results from meta-analysis of previous randomized trials[3] to assess the robustness of our findings. The evidence-based prior allowed us to formally incorporate prior clinical knowledge into the posterior estimates, enhancing the interpretability and strength of the evidence. This re-analysis demonstrated high probabilities of benefit (rVE >0%) for both P/I and all-cause mortality across all priors, and high probabilities (>90%) of achieving rVE >10%, supporting the consistency of the observed treatment effects. For cardiorespiratory hospitalization, the probabilities of rVE >10% were moderate (49% to 62%), while for all-cause hospitalization, the probabilities were low (25% to 32%), suggesting more limited or uncertain effects in these broader hospitalization outcome categories.

Beyond its ability to incorporate prior information, the Bayesian approach offers several interpretive advantages that are relevant for randomized controlled trials. Unlike traditional frequentist methods, which are typically used to conduct dichotomized significance tests and produce confidence intervals that are difficult to interpret, Bayesian analysis yields posterior probabilities that directly answer clinically meaningful questions – such as the probability that a treatment offers benefit or reduces risk by a certain amount.[9] This may offer more clear, more intuitive evidence than p-values and may increase confidence in decision-making. Moreover, the use of different prior distributions allows for formal sensitivity analyses, illustrating how robust the conclusions are to varying assumptions. Importantly, RCTs are seldom conducted without previous hypothesis-generating data; rather, they build upon a foundation of existing knowledge. Thus, incorporating informative priors into Bayesian analyses allows researchers to formally integrate prior evidence with new data, offering a more comprehensive and contextually grounded interpretation of trial outcomes. In the context of DANFLU-1, we found high posterior probabilities of benefit across all priors for both all-cause mortality and hospitalization for P/I, indicating robustness of results. Our results highlight the potential value of Bayesian methods, especially when sample sizes limit power for rare clinical outcomes. By quantifying the probability of clinically meaningful effects across a range of plausible priors, Bayesian re-analyses can offer decision-makers a more interpretable and policy-relevant understanding of vaccine benefits. This approach may support more accurate and timely public health decision-making.

There are, however, important considerations regarding the limitations of Bayesian analysis. Priors can exert a significant influence on posterior results, and their specification therefore requires careful consideration. This is particularly true for evidence-based priors, which must be derived from high-quality and representative data to avoid bias. In our study, we sought to define an evidence-based prior using only randomized controlled trial data that were available at the time of the DANFLU-1 trial, explicitly excluding observational studies to minimize the risk of unmeasured confounding influencing the prior – and thus the posterior – estimates. Nonetheless, some degree of subjectivity is inherent in the selection and specification of priors. The skeptical prior, for example, is also based on judgment, as it requires a decision about what constitutes a skeptical stance on the expected treatment effect. This may vary depending on the population, intervention, and clinical context. In this analysis, we reasoned that defining the skeptical prior such that there was only a 10% probability of an rVE of 10% or more provided a reasonable representation of clinical skepticism. Beyond the Bayesian framework, it is also important to note that the original DANFLU-1 trial was a feasibility study designed to assess implementation outcomes, with limited statistical power for detecting differences in clinical endpoints. In this context, our Bayesian re-analysis provides a valuable complementary perspective by quantifying the probability of clinically meaningful vaccine benefit. Notably, the probability of a >10% risk reduction exceeded 90% for both all-cause death and pneumonia/influenza hospitalization across all prior specifications, demonstrating the robustness of these findings despite the trial's limited power. These results illustrate how Bayesian methods can enhance interpretation and support clinical inference. Finally, the present analysis was conducted post hoc. Therefore, while the Bayesian re-analysis of this feasibility trial offers important insights, the findings should be interpreted with caution and confirmed through Bayesian analyses of fully powered randomized trials.

Conclusion

In this Bayesian re-analysis of the DANFLU-1 trial we observed high probabilities of reduced all-cause mortality and hospitalization due to pneumonia or influenza across all prior specifications. The

probabilities of rVE >10% were high, ranging from 91% to nearly 100%, indicating robust findings supportive of clinical benefit. However, as DANFLU-1 was a feasibility trial not powered for clinical outcomes, these findings should be interpreted with appropriate caution and warrant further investigation in future, adequately powered individually randomized trials using Bayesian methodologies to further validate these clinical benefits.

Author contributions

CRediT: **Daniel Modin:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing; **Niklas Dyrby Johansen:** Conceptualization, Investigation, Methodology, Writing – review & editing; **Anders Granholm:** Methodology, Writing – review & editing; **Brian L. Claggett:** Methodology, Writing – review & editing; **Joshua Nealon:** Project administration, Writing – review & editing; **Sandrine Samson:** Project administration, Writing – review & editing; **Matthew M. Loiacono:** Conceptualization, Methodology, Project administration, Resources, Writing – review & editing; **Rebecca C. Harris:** Methodology, Project administration, Resources, Writing – review & editing; **Carsten Schade Larsen:** Investigation, Writing – review & editing; **Anne Marie Reimer Jensen:** Data curation, Writing – review & editing; **Nino Emanuel Landler:** Data curation, Writing – review & editing; **Scott D. Solomon:** Methodology, Writing – review & editing; **Martin J. Landray:** Methodology, Writing – review & editing; **Gunnar H. Gislason:** Project administration, Resources, Writing – review & editing; **Lars Køber:** Methodology, Writing – review & editing; **Pradeesh Sivapalan:** Project administration, Resources, Writing – review & editing; **Jens Ulrik Stæhr Jensen:** Methodology, Project administration, Resources, Software, Writing – review & editing; **Tor Biering-Sørensen:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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COI: JN, SS, MML, and RCH are full-time employees of Sanofi and may hold stocks and/or shares in the company.

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