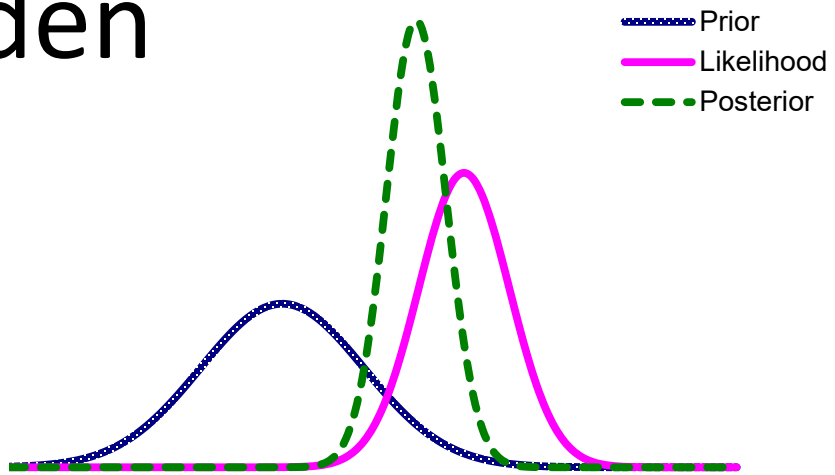
ZHAW Statistiker:innen Treffen 2022

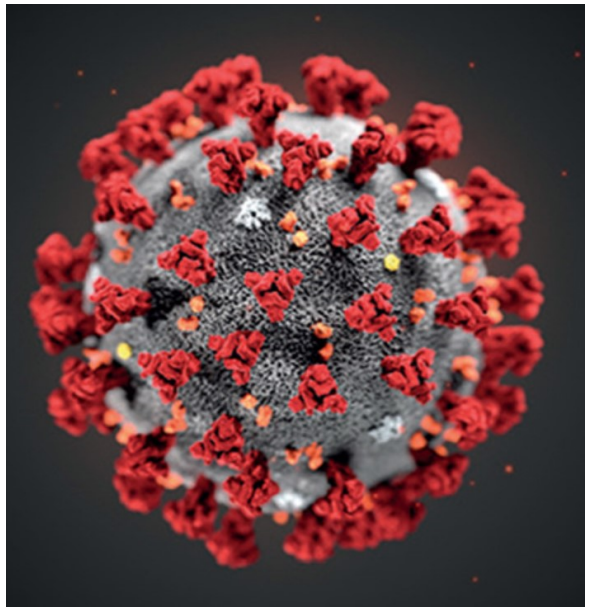
Wirksamkeitsvergleich von Covid 19-Impfstoffen mit einfachen Bayes-Methoden

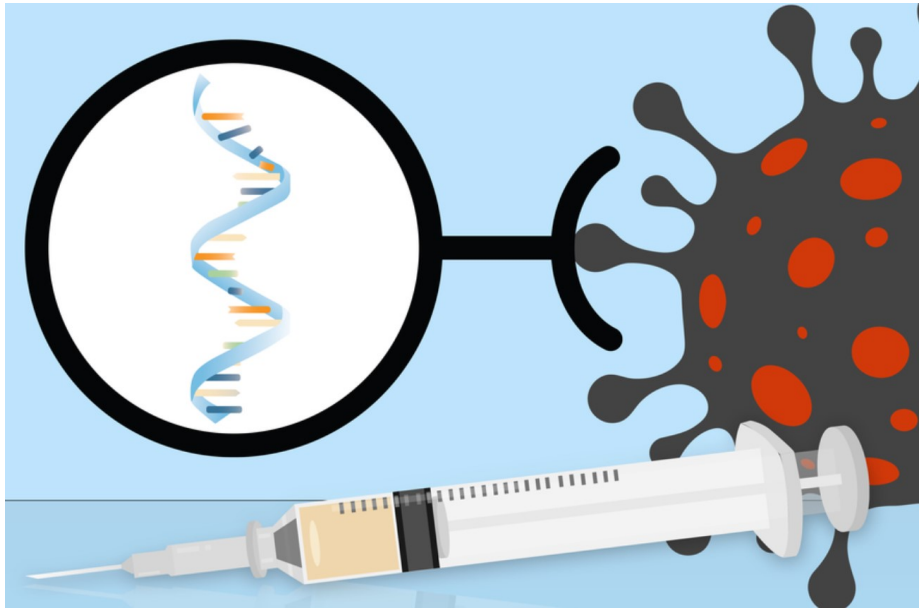


Yves-Laurent Grize
ZHAW School of Engineering
Winterthur Switzerland

Motivation?

Dezember 2020 …





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

This article was published on December 10, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2034577

STATISTICAL ANALYSIS

The safety analyses included all participants who received at least one dose of BNT162b2 or placebo. The findings are descriptive in nature and not based on formal statistical hypothesis testing. Safety analyses are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for local reactions, systemic events, and any adverse events after vaccination, according to terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1, for each vaccine group.

Analysis of the first primary efficacy end point included participants who received the vaccine or placebo as randomly assigned, had no evidence of infection within 7 days after the second dose, and had no major protocol deviations (the population that could be evaluated). Vaccine efficacy was estimated by $100 \times (1 - \text{IRR})$, where IRR is the calculated ratio of confirmed cases of Covid-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group. The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%.

The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model.

Kurzes Review: Bayesianische Inferenz - 1

der Erfinder

der Rechner

$$P(B|A) = \frac{P(A|B)\,P(B)}{P(A)}$$

$$f_{\theta|X=x}(\theta) = \frac{f_{X|\Theta=\theta}(x) f_{\Theta}(\theta)}{\int_{-\infty}^{+\infty} f_{X|\Theta=\theta}(x)\; f_{\Theta}(\theta) d\theta}$$

die Anwendung

$X \sim Bin(n, \theta)$	$\theta \sim Beta(\alpha, \beta)$	$\theta \mid X \sim Beta(\alpha'(X), \beta'(X))$ $\alpha'(x) = \alpha + x$ $\beta'(x) = n + \beta - x$

Kurzes Review: Bayesianische Inferenz - 2

Beispiel

Eine Münze wird 10 Mal geworfen, jedesmal kommt Zahl vor.

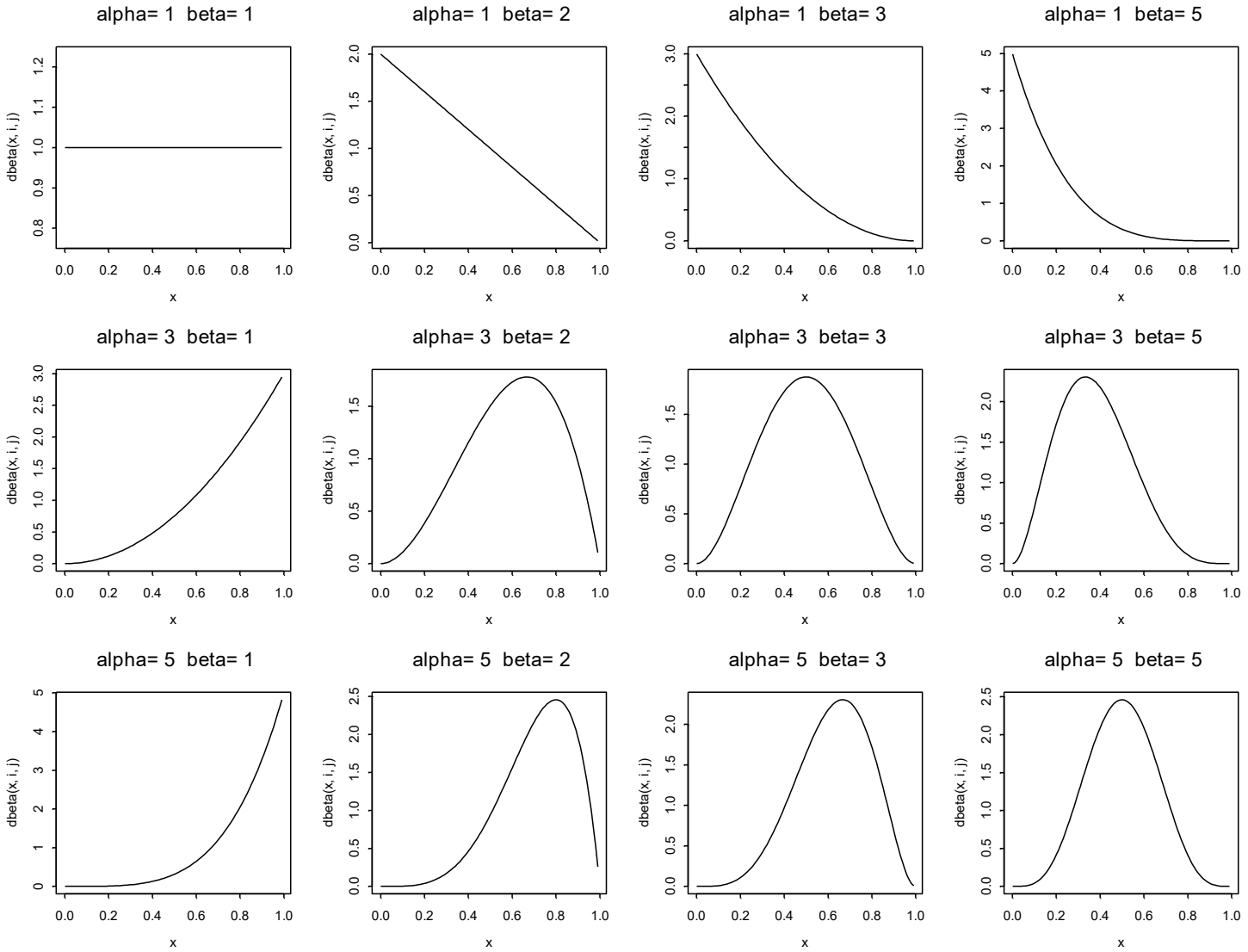
Frage: wie gross ist die Wahrscheinlichkeit, dass Kopf beim 11. Wurf vorkommt?

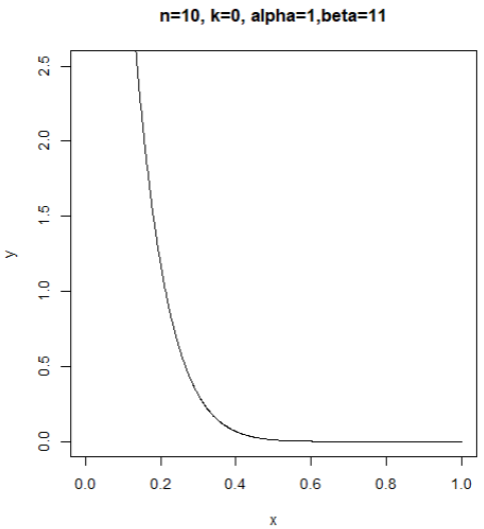
Kurzes Review: Bayesianische Inferenz - 3

Die bessere Antwort: Kombination von Erfahrung und Daten

Verteilung der Daten:	Sei X die Anzahl von “Kopf” X gegeben θ folgt eine Binomialverteilung Bin(n, θ)
A-priori Wissen:	z. B. totale Ignoranz d.h. θ ist gleichmassig zwischen 0 und 1 verteilt: θ ~Beta(1,1)
A-posteriori Wissen gegeben X=k:	die a-posteriori Verteilung von θ ist die Beta-Verteilung Beta(k+1, n+1-k) mit Erwartungswert (k+1)/(n+2) Bemerkung: Der Schätzer (k+1)/(n+2) trägt den Namen: „Laplace Rule of Succession“.
Anwendungsfall:	Fall n=10 und k=0 → θ ~ Beta(0+1, 10+1-0) = Beta(1,11) Erwartungswert der a-posteriori Verteilung von θ = 1/12 ≈ 0.08

Kurzes Review: Einige Beta-Verteilungen Beta(α, β) auf Träger [0, 1]





Bayesianische Schätzmethoden für die Wirksamkeit von Covid-19 Impfungen

Zurich University of Applied Sciences

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Efficacy=

1 - infection rate in vaccine group/ infection rate in placebo

The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model.

Table 2. **Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.***

The Data

The Results

Efficacy End Point	BNT162b2 No. of Cases	BNT162b2 Surveillance Time (n)†	Placebo No. of Cases	Placebo Surveillance Time (n)†	Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (1,7411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.

† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.

‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

Bayesianische Schätzmethoden für die Wirksamkeit von Covid-19 Impfungen

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Zurück zur Beta_Binomial Model:

X_1=Anzahl Covid-Fälle in der Gruppe 1 (Impfung-Gruppe) Θ_1= infectionsrate in Gruppe 1 ~Beta(1,1)

X_2=Anzahl Covid-Fälle in der Gruppe 2 (Placebo-Gruppe) Θ_2= infectionsrate in Gruppe 2 ~Beta(1,1)

Alle Zufallssvariablen unabhängig vorausgesetzt

Wirksamkeit = 1- Θ_1/ Θ_2

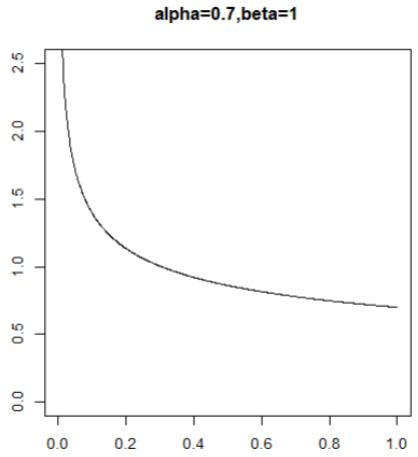
Inferenz über Wirksamkeit? -> kein Problem in der Bayes-Statistik!

Simuliere aus der (hier exakt bekannten) a-posteriori Verteilungen von Θ_1 und Θ_2, bilde die Wirksamkeit und verwende Monte-Carlo Schätzungen für den 95% Kredibilitätsbereich oder für Wirksamkeit>30%

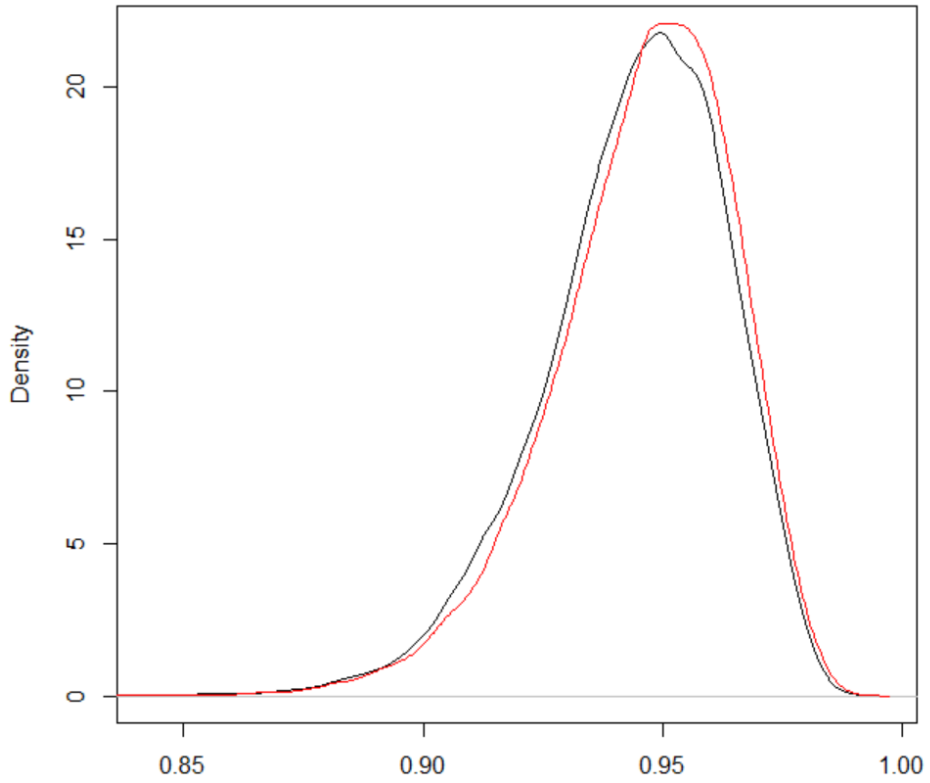
Comparison with the prior used by BionTech: Effect on the posterior probability distributions

Black: Beta-Binomial with a uniform prior
95%- Cred. Interv.
2.5% 50% 97.5%
0.901 0.946 0.975

Red: Beta-Binomial with a Beta(0.7,1) prior
95%- Cred. Interv.
2.5% 50% 97.5%
0.903 0.948 0.976



→ verwende weiter Beta(1,1) als a-priori Verteilung.



Wirksamkeitsvergleich: BionTech vs. Moderna

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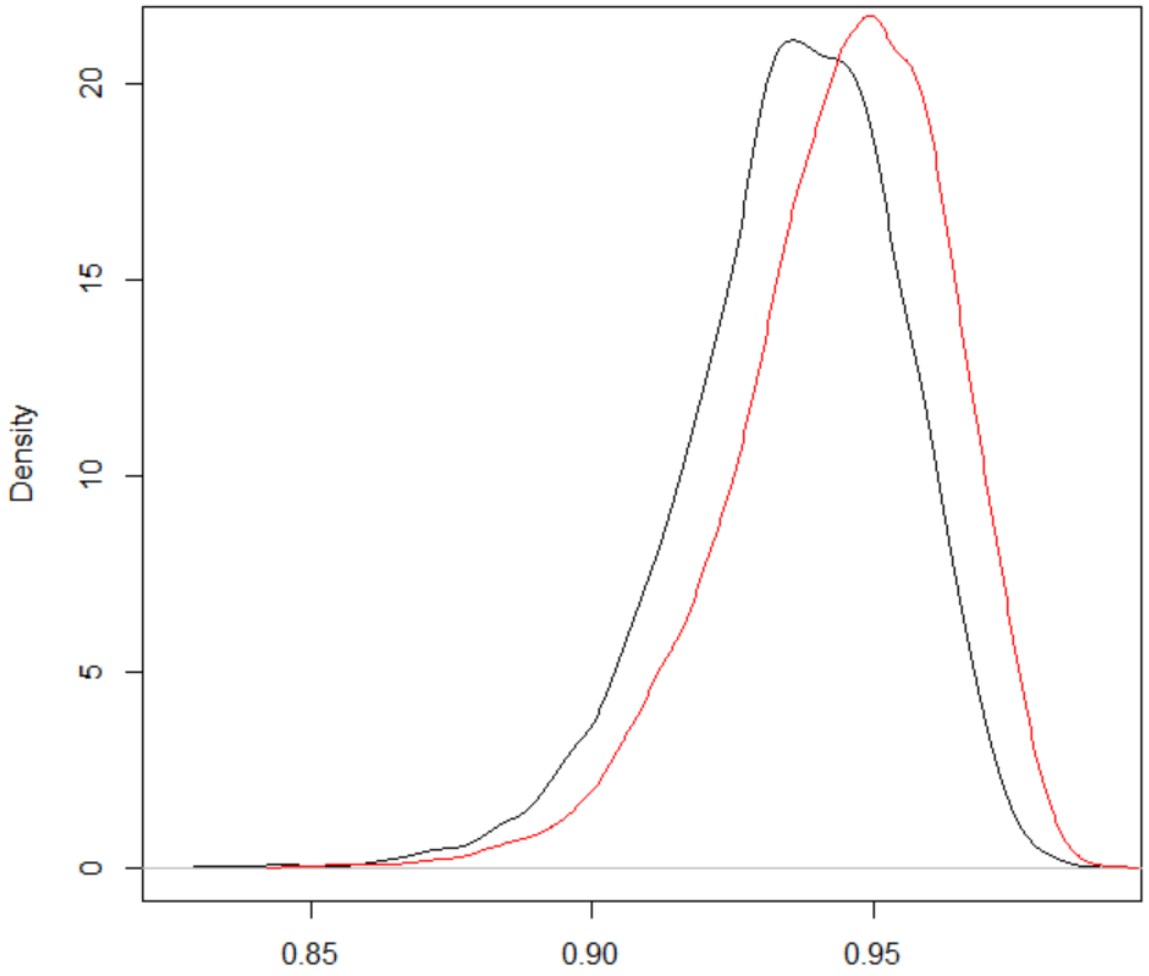
Efficacy: Red BionTech Black Moderna



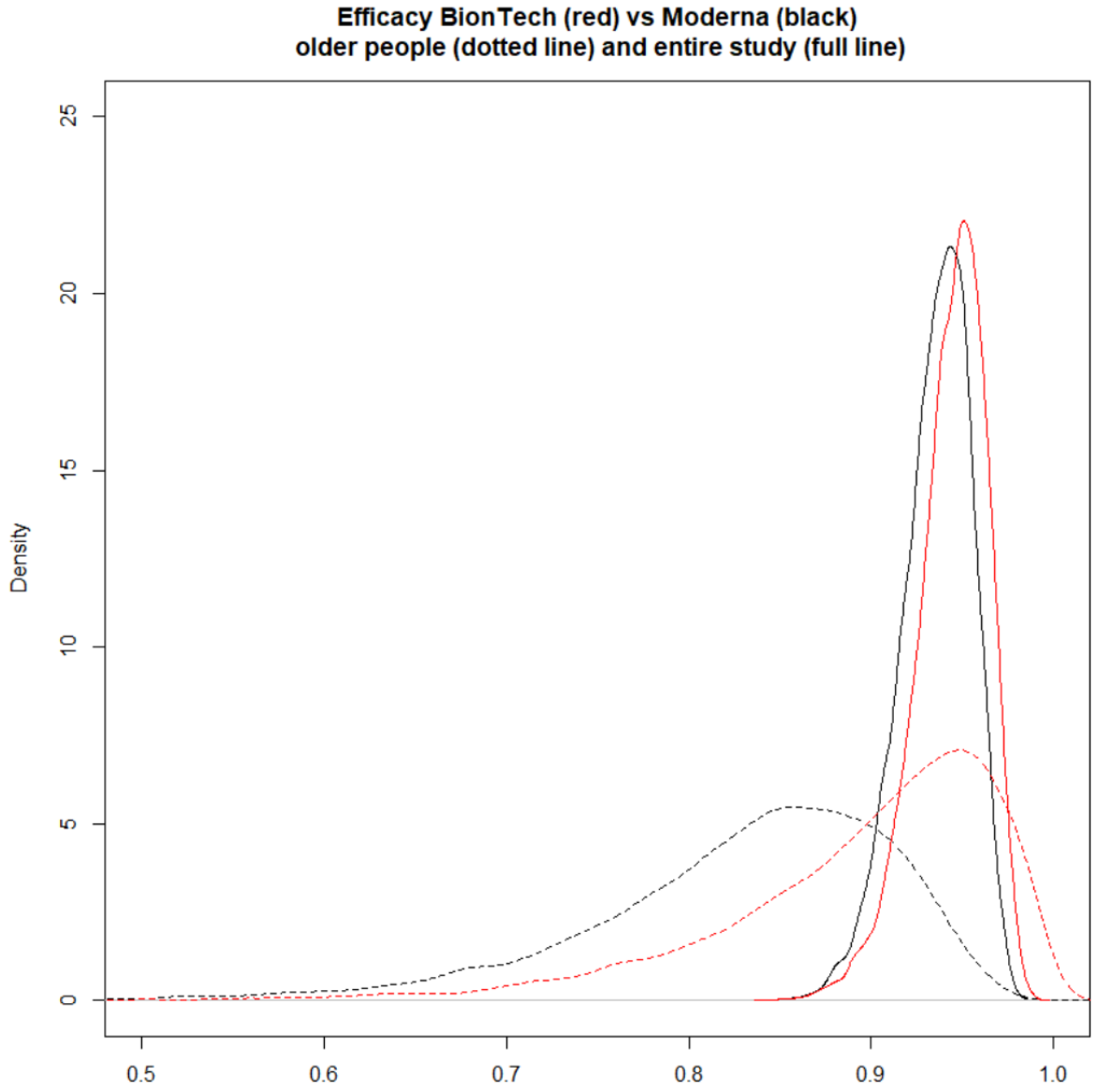
BionTech
95%CrI:
2.5% 50% 97.5%
0.901 0.946 0.975
Mean: 0.944

Moderna:
95%CrI:
2.5% 50% 97.5%
0.893 0.937 0.968
Mean: 0.935

Wirksamkeitsvergleich: BionTech vs. Moderna
Unterschiedliche Altersgruppen

	with vaccine		Placebo	
Entire study	Cases	Sample (N)	Cases	Sample (N)
Pfizer	8	18198	162	18325
Moderna	11	14134	185	14073
Older people	Cases	Sample (N)	Cases	Sample (N)
Pfizer	1	3848	19	3880
Moderna	4	3583	29	3552

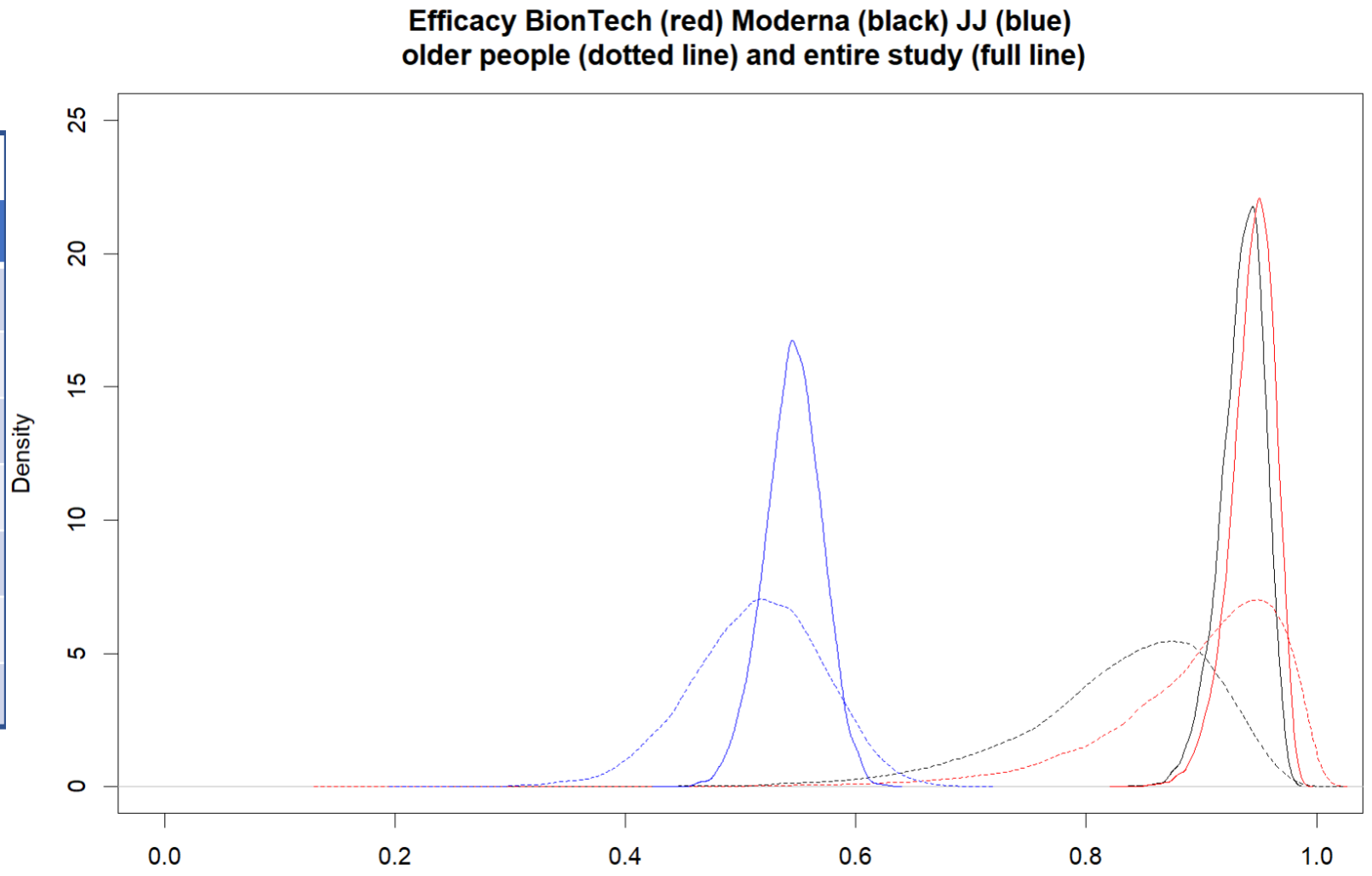
Model: Beta-Binomial with a uniform prior (i.e. beta(1,1))
Older people = “> 65y”



Wirksamkeitsvergleich: BionTech vs. Moderna vs. Janssen mit unterschiedlichen Altersgruppen

	with vaccine		Placebo	
Entire study	Cases	N	Cases	N
Pfizer	8	18198	162	18325
Moderna	11	14134	185	14073
Janssen*	484	19400	1067	19398
Older people				
Pfizer	1	3848	19	3880
Moderna	4	3583	29	3552
Janssen*	103	5812	220	5963

*: Jannsen's published numbers are not directly comparable to BionTech/Moderna. Here using grouping: moderate to severe.
Janssen ist ein Vektor-Impfung mit 1 Dosis.



Zusammenfassung

- **Mit der Bayes-Statistik:**
  1) **Komplexe Fragestellungen können einfach behandelt werden**
  2) **Dank der Visualisierung der a-posteriori Verteilungen stehen informative grafische Darstellungen für die Inferenz zur Verfügung**

- **Dieses recht aktuelles Beispiel ist sehr geeignet für einen Einführungskurs in der Bayes Statistik**

Zu guter Letzt noch zwei Neuigkeiten über Wahrscheinlichkeit, Inferenz und Bayes …

Bayesian Statistics and Neuroscience: the Bayesian Brain

If you are interested and have 15mn to spare, watch this video:
the Free Energy Principle with neuroscientist Karl Friston
on the Markov blanket, Bayesian model evidence, and different global brain theories

Active Inference:
The Free Energy Principle in Mind, Brain, and Behavior

(erschienen 29. März 2022)

In short:
the brain uses a gradient descent algorithm on free-energy (a bound to the surprise on sampling data from a generative model) to optimize action and perception

Parrots understand probability

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sciencealert Trending

(Amalia Bastos)

NATURE

Parrots Are Only The Second Kind of Animal We've Found That Can Grasp Probabilities

DAVID NIELD 3 MARCH 2020

Up until now, only human beings and other great apes have demonstrated an ability to understand probabilities – being able to weigh up the odds based on the available data, or statistical inference, as it's formally called. Now, for the first time, a parrot species has demonstrated this skill.

Tests on six kea (*Nestor notabilis*) parrots have shown they were able to understand and act on probabilities in a variety of scenarios that have previously been tested on humans and apes.

The findings have some wide-reaching implications – from understanding more about how the minds of non-primates might work, to producing more realistic and detailed artificial intelligence systems of our own.

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Article | Open Access | Published: 03 March 2020

Kea show three signatures of domain-general statistical inference

Amalia P. M. Bastos ✉ & Alex H. Taylor

A kea parrot and sample jars. (Amalia Bastos)

Zurich University
of Applied Sciences

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THANK YOU

for your

ATTENTION!

Literature

Safety and Efficacy of BNT162b2 m-RNA Covid-19 Vaccine, NEJM.org, 12/12/2020 or
The New England Journal of Medicine Vol.383, No.27, 31.12.2020

Safety and Efficacy of mRNA-1273 SARS-Cov-2 Vaccine, The New England Journal of Medicine Vol.384, No.5, 04.02.2021

Final Analysis of Efficacy and Safety of Single-Dose Ad26.COV2.S, The New England Journal of Medicine Vol.386, No.9, 03.03.2022

BAG Recommendations

Vaccine	Approved for age	Vaccination schedule for initial immunisation
Pfizer/BioNTech	From age 12	2 doses at an interval of around four weeks
Pfizer/BioNTech children's vaccine	5 - 11 years	2 doses at an interval of around four weeks
Moderna	From age 12	2 doses at an interval of around four weeks
Janssen	From age 18	1 dose*
Novavax	From age 18	2 doses at an interval of around four weeks

*For better protection, we recommend that between 28 days to 4 months after vaccination you supplement the initial immunisation with a dose of an mRNA vaccine from Moderna or Pfizer/BioNTech.

Are you over 18? In this case, if you can't be vaccinated with an mRNA vaccine for medical reasons or if you refuse mRNA vaccines, you can be vaccinated with Janssen's vector vaccine or the protein vaccine from Novavax.