Anhang zur wissenschaftlichen Begründung der STIKO-Empfehlung zur Auffrischimpfung von Personen ≥12 Jahren mit einem Omikron-BA.1-adaptierten bivalenten mRNA-Impfstoff

Inhalt

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1.1 Zulassungstudie des Omikron-BA.1-adaptierten bivalenten Impfstoffs Comirnaty Original/Omicron BA.1) von BioNTech/Pfizer

Das Verzerrungsrisiko wurde mit dem aktualisierten Risk of Bias Tool (RoB 2) bewertet (1). Die Bias-Kriterien werden mit „niedrig“, „einige Bedenken“ und „hoch“ bewertet.

Outcome	Randomization Process	Deviations from intended interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the reported result	Overall Bias
SARS-CoV-2 Infections	..	..	..	..	..	..
Symptomatic COVID-19	Some concern[1]	Some concern[2]	High[3]	Some concern[5]	Low	High
Severe COVID-19	Some concern[1]	Some concern[2]	High[3]	Some concern[5]	Low	High
Neutralising antibodies	Some concern[1]	Some concern[2]	Low[4]	Low[6]	Low[7]	Some concern
Local reactions	Some concern[1]	Some concern[2]	Low[4]	Low	Low[7]	Some concern
Systemic reactions	Some concern[1]	Some concern[2]	Low[4]	Low	Low[7]	Some concern
AESIs	Some concern[1]	Some concern[2]	Low[4]	Low	Low[7]	Some concern
AEs	Some concern[1]	Some concern[2]	Low[4]	Low	Low[7]	Some concern
SAEs	Some concern[1]	Some concern[2]	Low[4]	Low	Low[7]	Some concern

[1] no information about randomization methods, but no imbalances are apparent.

[2] unblinded personnel administered vaccination but side effects are not specific to one of the interventions; no intention-to-treat (ITT) analyses is presented.

[3] data of COVID-19 cases with cut-off date of 16.05.2022; unclear why no updated case-number are available until now

[4] no information about missing outcome data

[5] self-assessment of COVID-19 symptoms with subsequent PCR confirmation; observer-blinded study, but unblinded personnel administered intervention and could have informed study participants consciously or unconsciously about treatment assignment.

[6] knowledge of treatment assignment possible; however standard lab procedures performed and therefore measurement probably robust to awareness of intervention

[7] all evaluated outcomes were assessed and reported as defined in the study protocol.

1.2 Zulassungstudie des Omikron-BA.1-adaptierten bivalenten Impfstoffs Spikevax bivalent Original/Omicron BA.1 von Moderna

Das Verzerrungsrisiko wurde mit dem *Risk Of Bias In Non-randomized Studies - of Interventions* (ROBINS-I) Tool bewertet (2). Die Bias-Kriterien werden mit „niedrig“, „moderat“, „schwer“ und „kritisch“ bewertet.

Outcome	Confounding	Participant Selection	Deviations from intended interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the reported result	Overall Bias
SARS-CoV-2 Infections	Critical[1]	Moderate[2]	Low	Serious[3]	Low[4]	Moderate[5]	Critical
Symptomatic COVID-19	Critical[1]	Moderate[2]	Low	Serious[3]	Low[4]	Moderate[5]	Critical
Severe COVID-19	..	..	..	..	..	..	..
Neutralising antibodies	Serious[6]	Low[7]	Low	Serious[8]	Low[9]	Moderate[10]	Serious
Local reactions	Critical[1]	Low[7]	Low	Moderate[11]	Moderate[12]	Low	Critical
Systemic reactions	Critical[1]	Low[7]	Low	Moderate[11]	Moderate[12]	Low	Critical
AESIs	Critical[1]	Low[7]	Low	Moderate[11]	Moderate[13]	Low	Critical
AEs	Critical[1]	Low[7]	Low	Moderate[11]	Moderate[13]	Low	Critical
SAEs	Critical[1]	Low[7]	Low	Moderate[11]	Low[14]	Low	Critical

[1] no adjustments performed and differences between groups (e.g. sex, SARS-CoV-2 status) could have a substantial impact on the outcome.

[2] sequential recruitment - participants in control group were followed a median of 57 days and participants in intervention group 43 days, but differences taken into consideration through calculation of incidence rates per person-weeks.

[3] 339/437 (76%) participants of intervention group and 266/377 (70%) participants of control group who received injection evaluated (per-protocol set for efficacy: all participants in the FAS who receive the planned dose of study vaccination, who are SARS-CoV-2 negative at baseline) data for participants with positive SARS-COV-2 status at baseline not reported.

[4] active surveillance of participants through weekly contact and blood draws.
[5] Vaccine efficacy not formally assessed in this trial; IRR reported but not previously planned.
[6] GMT against ancestral strain and BA.1 adjusted for age group and pre-booster titers, GMT against BA.4/5 not adjusted.
[7] sequential recruitment, but probably no impact on outcome.
[8] Per-Protocol (PP) Set for Immunogenicity evaluated for primary outcome, adjusted GMTs and GMRs not available for ITT population.
[9] standard lab procedure used for outcome measurement.
[10] ID50 and ID80 titers reported and not defined in available extract of protocol, which was planned to be used for primary analysis
[11] all participants of intervention group that received at least one dose evaluated, but only 351/377 (93%) participants of control group. Missing data could have a small impact on the true effect
[12] self-reported outcome and knowledge of treatment assignment. Due to subjectiveness of outcome, influence through awareness of assignment possible
[13] probably self-reported outcome and knowledge of treatment assignment. Due to subjectiveness of outcome, influence through awareness of assignment possible
[14] Due to severity of outcome, no influence through awareness of assignment expected

2. Risk of Bias-Bewertung BA.4/BA.5-adaptierte bivalente Impfstoffe

Das Verzerrungsrisiko wurde mit dem *SYstematic Review Centre for Laboratory animal Experimentation* (SYRCLE) Tool, dass eigens für die Beurteilung tierexperimenteller Studien entwickelt wurde (3). Die Bias-Kriterien werden mit „niedrig“, „hoch“ und „unklar“ bewertet.

2.1 Zulassungsstudie des Omikron-BA.4/BA.5-adaptierten bivalenten Impfstoffs Comirnaty Original/Omicron BA.4/5 von BioNTech/Pfizer

Outcome	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Other	Overall Bias
	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	
SARS-CoV-2 Infection	..	..	..	..	..	..	..	..	..	..	..
Symptomatic COVID-19	..	..	..	..	..	..	..	..	..	..	..
Severe COVID-19	..	..	..	..	..	..	..	..	..	..	..
Neutralising antibodies	Unclear[1]	Unclear[1]	Unclear[1]	Unclear[1]	Unclear[1]	Unclear[1]	Unclear[1]	Unclear[2]	Unclear[3]	High[4]	High
Local reactions	..	..	..	..	..	..	..	..	..	..	..
Systemic reactions	..	..	..	..	..	..	..	..	..	..	..
AESIs	..	..	..	..	..	..	..	..	..	..	..
AEs	..	..	..	..	..	..	..	..	..	..	..
SAEs	..	..	..	..	..	..	..	..	..	..	..

[1] no information provided

[2] reported that 10 mice allocated to each group, but no information provided on how many mice were evaluated per respective intervention

[3] Neutralizing Titer before and after intervention reported for different vaccines and against different variants, but no direct comparison of antibody increases possible due to missing data.

[4] data available from presentation of vaccine manufacturer only and protocol adherence, etc. Comparison with prototype vaccine not conducted.

2.2 Zulassungsstudie des Omikron-BA.4/5-adaptierten bivalenten Impfstoffs Spikevax bivalent Original/Omicron BA.4/5 von Moderna

Outcome	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Other	Overall Bias
	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	
SARS-CoV-2 Infections	..	..	..	..	..	..	..	..	..	..	..
Symptomatic COVID-19	..	..	..	..	..	..	..	..	..	..	..
Severe COVID-19	..	..	..	..	..	..	..	..	..	..	..
Neutralising antibodies	High[1]	Unclear[2]	High[1]	Unclear[3]	High[1]	High[1]	High[1]	Low	High[3]	Low	High
Local reactions	..	..	..	..	..	..	..	..	..	..	..
Systemic reactions	..	..	..	..	..	..	..	..	..	..	..
AESIs	..	..	..	..	..	..	..	..	..	..	..
AEs	..	..	..	..	..	..	..	..	..	..	..
SAEs	..	..	..	..	..	..	..	..	..	..	..

1: Quote: “Experiments were neither randomized nor blinded”

2: few information provided, but all mice female and 7-weeks old

3: Quote: “Animals were housed in groups and fed standard chow diets.”; Comment: no details on groups provided

4: EC50 Titer before and after intervention reported for different vaccines and against different variants, but no confidence intervals reported.

3. Literaturverzeichnis

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