Anhang zur wissenschaftlichen Begründung der STIKO-Empfehlung zur Impfung gegen COVID-19 mit dem Impfstoff Nuvaxovid (Novavax)

Inhalt

1. Syntax der Suchstrategie zu COVID-19

Die systematische Literaturrecherche erfolgte in der COVID-19 Literaturdatenbank der Bibliothek des RKI. Diese erfasst sämtliche COVID-19-relevanten Einträge in den Datenbanken Pubmed und Embase (inkl. Medline) sowie auf den Pre-Print Servern ArRvix, BioRvix, ChemRvix, MedRvix, Preprints.org, ResearchSquare und SSRN.

Search Syntax PubMed 1:
("Severe Acute Respiratory Syndrome Coronavirus 2" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "COVID 19 diagnostic testing" [Supplementary Concept] OR "COVID 19 drug treatment" [Supplementary Concept] OR "COVID 19 serotherapy"[Supplementary Concept] OR "COVID 19 vaccine" [Supplementary Concept] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[tiab] OR ncov*[tiab] OR COVID*[tiab] OR sars-cov-2[tiab] OR "sars cov 2"[tiab] OR "SARS Coronavirus 2"[tiab] OR "Severe Acute Respiratory Syndrome CoV 2"[tiab] OR "Wuhan coronavirus"[tiab] OR "Wuhan seafood market pneumonia virus"[tiab] OR "SARS2"[tiab] OR "2019-nCoV"[tiab] OR "hcov-19"[tiab] OR „novel 2019 coronavirus“[tiab] OR "2019 novel coronavirus*"[tiab] OR „novel coronavirus 2019*“[tiab] OR "2019 novel human coronavirus*"[tiab] OR „human coronavirus 2019“[tiab] OR "coronavirus disease-19"[tiab] OR "corona virus disease-19"[tiab] OR "coronavirus disease 2019"[tiab] OR "corona virus disease 2019"[tiab] OR "2019 coronavirus disease"[tiab] OR "2019 corona virus disease"[tiab] OR „novel coronavirus disease 2019“[tiab] OR „novel coronavirus infection 2019“[tiab] OR "new coronavirus*"[tiab] OR "coronavirus outbreak"[tiab] OR "coronavirus epidemic"[tiab] OR "coronavirus pandemic"[tiab] OR "pandemic of coronavirus"[tiab]) AND ("2019/12/01"[PDAT] : "2099/12/31"[PDAT])

Search Syntax PubMed 2:
("wuhan"[tiab] or china[tiab] or hubei[tiab]) AND ("Severe Acute Respiratory Syndrome Coronavirus 2"[Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "COVID 19 diagnostic testing"[Supplementary Concept] OR "COVID 19 drug treatment"[Supplementary Concept] OR "COVID 19 serotherapy"[Supplementary Concept] OR "COVID 19 vaccine"[Supplementary Concept] OR "coronavirus*"[tiab] OR "corona virus*"[tiab] OR ncov[tiab] OR COVID*[tiab] OR sars*[tiab])

Search Syntax Embase 1:
('severe acute respiratory syndrome coronavirus 2':ti,ab OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'COVID 19'/exp OR ncov*:ti,ab OR COVID*:ti,ab OR 'sars cov 2':ti,ab OR 'sars-cov-2':ti,ab OR 'sars coronavirus 2':ti,ab OR 'sars coronavirus 2'/exp OR 'severe acute respiratory syndrome cov 2':ti,ab OR 'wuhan coronavirus':ti,ab OR 'wuhan seafood market pneumonia virus':ti,ab OR sars2:ti,ab OR '2019-ncov':ti,ab OR 'hcov-19':ti,ab OR 'novel 2019 coronavirus':ti,ab OR '2019 novel coronavirus*':ti,ab OR 'novel coronavirus 2019'/exp OR '2019 novel human coronavirus*':ti,ab OR 'human coronavirus 2019':ti,ab OR 'coronavirus disease-19':ti,ab OR 'corona virus disease-19':ti,ab OR 'coronavirus disease 2019':ti,ab OR 'coronavirus disease 2019'/exp OR 'corona virus disease 2019':ti,ab OR '2019 coronavirus disease':ti,ab OR 'novel coronavirus 2019*':ti,ab OR 'novel coronavirus disease 2019':ti,ab OR 'novel coronavirus infection 2019':ti,ab OR '2019 corona virus disease':ti,ab OR 'new coronavirus*':ti,ab OR 'coronavirus outbreak':ti,ab OR 'coronavirus epidemic':ti,ab OR 'coronavirus pandemic':ti,ab OR 'pandemic of coronavirus':ti,ab OR 'severe acute respiratory syndrome coronavirus 2 vaccine'/exp OR 'COVID 19 vaccine'/exp) AND 2020:py

Search Syntax Embase 2:
(wuhan:ti,ab OR china:ti,ab OR hubei:ti,ab) AND ('severe acute respiratory syndrome coronavirus 2':ti,ab OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome coronavirus 2' OR 'COVID*':ti,ab OR 'COVID 19'/exp OR 'COVID 19' OR coronavirus*:ti,ab OR 'corona virus*':ti,ab OR ncov:ti,ab OR COVID*:ti,ab OR sars*:ti,ab OR 'sars coronavirus 2'/exp)

Manual search in ArRvix, BioRvix, ChemRvix, MedRvix, Preprints.org, ResearchSquare und SSRN

Suchstrategie in der RKI-Datenbank zur Erfassung der Evidenz zur Impfung mit Novaxuvid (Datum der Suche: 22.12.21)

Ziel der Suchstrategien war es, Originalarbeiten zur Wirksamkeit und Sicherheit der Impfung mit Novaxuvid der Firma Novavax zu erhalten. Hierfür wurde die Suchstrategie der Bibliothek (n= 311.745) mit den folgenden Suchstrategien kombiniert:

Suche	Oberbegriffe	Suchstring	Treffer
#1	Impfung, Impfstoff	Vaccine* OR Immuniz* OR Immunis*	33.901
#2	Novaxuvid	NVX-CoV2373 OR Nuvaxovid Or Novavax	53
Nach Screening Titel, Abstract und Volltext			17

Die systematische Suche wurde durch eine Handsuche ergänzt.

2. PICO-Fragen zur Beratung der Empfehlung der Impfung mit NVX-CoV2373

Tabelle 1: PICO-Fragen zur Wirksamkeit bzw. Sicherheit der Impfung mit NVX-CoV2373

Population	Gesamte Bevölkerung Spezielle Sub- und Altersgruppen nach Priorisierung Erwachsene im Alter ≥ 18 Jahre Kinder und Jugendliche	
Intervention	**COVID-19-Impfung** mit (NVX-CoV2373) von Novavax	
Comparator (Vergleichs-intervention)	- keine Impfung - Placebo oder Impfung gegen einen anderen Erreger (z.B. Meningokokken) - anderer COVID-19-Impfstoff (*head to head*-Vergleich)	
Outcome	**Wirksamkeit** - SARS-CoV-2*-Infektion - COVID-19*-Erkrankung, symptomatisch - COVID-19*-Hospitalisierung - COVID-19*, ITS-pflichtig - COVID-19*, beatmungspflichtig - COVID-19*-bedingter Tod - Dauer des Schutzes - Wirksamkeit bei nur einer Impfung *labordiagnostisch gesichert (PCR)	**Sicherheit** - Lokalreaktionen - Systemische Reaktionen - Schwere unerwünschte Impfstoffwirkungen (UAW) - UAW von speziellem Interesse - Verstärkung einer nachfolgenden SARS-CoV-2 Infektion bzw. Verschlimmerung des Verlaufs einer COVID-19-Erkrankung („Enhanced COVID-19)

3. Wichtigkeit der Endpunkte, die im Systematischen Review betrachtet werden

Tabelle 2: Endpunkte zur Wirksamkeit des Impfstoffs

Wirksamkeit	Bewertung
SARS-CoV-2 Infektion*	wichtig
COVID-19*- Erkrankung* (milde bis schwer)	wichtig
COVID-19*- Erkrankung* schwer	wichtig
COVID-19*- Hospitalisierung	kritisch
COVID-19*- Hospitalisierung (ITS-pflichtig)	kritisch
COVID-19*- Hospitalisierung (beatmungspflichtig)	kritisch
COVID-19*-bedingter Tod	kritisch
Wirksamkeit gegen Variant of Concern oder Variant of Interest	kritisch

*** labordiagnostisch gesichert mit PCR**

Tabelle 3: Endpunkte zur Sicherheit des Impfstoffs

Sicherheit	Bewertung
Lokalreaktionen (Schmerz, Schwellung, Rötung etc.)	wichtig
Systemische Reaktionen (Myalgien, Übelkeit, Kopfschmerzen, Abgeschlagenheit etc.)	wichtig
Schwere Impfstoffnebenwirkungen	kritisch
Adverse events of special interest (AESI) nach CEPI Kriterien, z.B. enhanced COVID-19, Myokarditiden, Guillian-Barré Syndrom, TTS.	kritisch

4. Risk of Bias-Bewertung: Randomisierte Studien zur Wirksamkeit und Sicherheit von Nuvaxovid

Study	Outcome	Randomization Process	Deviations from intended interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the reported result	Overall Bias
Heath 2021	Symptomatic COVID-19	Low	High[1]	Some concern[2]	Some concern[3]	Low	High
Heath 2021	Severe COVID-19	Low	High[1]	Some concern[2]	Low[4]	Low	High
Heath 2021	Hospital admission due to COVID-19	Low	High[1]	Some concern[2]	Low[4]	Some concern[5]	High
Heath 2021	Local reactions	Low	Some concern[6]	Some concern[7]	Some concern[8]	Some concern[9]	Some concern
Heath 2021	Systemic reactions	Low	Some concern[6]	Some concern[7]	Some concern[8]	Some concern[9]	Some concern
Heath 2021	AESIs (PIMMC and COVID-related)	Low	Low	Low	Some concern[8]	Some concern[10]	Some concern
Heath 2021	SAE (serious adverse events)	Low	Low	Low	Low	Some concern[10]	Some concern
Dunkle et al.	Symptomatic COVID-19	Low	High[11]	Low	Some concern[3]	Low	High
Dunkle et al	Severe COVID-19	Low	High[11]	Low	Low	Low	High
Dunkle et al	Local reactions	Low	Some concern[12]	Low	Some concern[8]	Low	Some concern
Dunkle et al	Systemic reactions	Low	Some concern[12]	Low	Some concern[8]	Low	Some concern
Dunkle et al	AESIs (PIMMC and COVID-related)	Low	Some concern[12]	Low	High[13]	Low	High
Dunkle et al	SAE (serious adverse events)	Low	Some concern[12]	Low	High[14]	Low	High

[1] unblinded personnel administered vaccination but deviations balanced between groups; per-protocol population analysed but unclear who was excluded due to protocol violations and substantial differences between ITT and PP-effect.

[2] per-protocol population analysed, but only 7020/7406 (vaccine); 7019/7403 (placebo) that received both doses as assigned and did not discontinue trial after second dose due to other reason evaluated; other protocol deviations justifying exclusion not clearly described, thus missingness could depend on true value.

[3] 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. "To maintain the blind, placebo vaccination via IM route will be included and unblinded site personnel will manage study vaccine".

[4] knowledge of treatment assignment possible; however due to severity of outcome influence through knowledge unlikely.

[5] reported outcome should include participants regardless of serostatus at baseline, but only includes PP-population/seronegative participants admission or mechanical ventilation linked to any virologically confirmed (by PCR to SARS-CoV-2) COVID-19 with onset at least 7 days after second study vaccination).
[6] unblinded personnel administered vaccination but deviations balanced between groups; subset of safety population analysed.
[7] subset of safety population evaluated; data for 2.310 of approx. planned 2400 included (96%); only percentages reported and unclear how many participants were evaluated per group
[8] self-reported outcome and knowledge of treatment assignment possible. Due to subjectiveness of outcome, influence through awareness of assignment possible
[9] reported as per protocol only for a subset of included participants; according to SAP safety subset planned for "approximately 2,000 participants and in the seasonal influenza vaccine co-administration sub-study of approximately 400 participants"
[10] reported up to data cutoff date of the final efficacy analysis (timepoint not reported); but planned for 28 days after dose 2
[11] unblinded personnel administered vaccination, deviations not balanced between groups (eg number of withdrawals and number with major protocol deviations almost the same despite 2:1 randomisation); per-protocol population analysed.
[12] unblinded personnel administered vaccination, deviations not balanced between groups (eg number of withdrawals and number with major protocol deviations almost the same despite 2:1 randomisation); Safety population (all participants that received at least one dose) analysed.
[13] self-reported outcome and knowledge of treatment assignment possible. Due to subjectiveness of outcome, influence through awareness of assignment possible; further, according to trial report duplicate reporting by investigators possible
[14] Due to objectiveness of outcome, influence through awareness of assignment unlikely; however, according to trial report duplicate reporting of unsolicited Aes (potentially including SAEs) by investigators possible.

5. GRADE Evidenzprofil: Impfung gegen COVID-19 mit Nuvaxovid

Population: previously non-vaccinated adult individuals (>= 18 years), with or without co-morbidities

Intervention: Nuvaxovid

Comparison: Placebo

Setting: Omicron as dominant circulating variant

Quality (Certainty) assessment							No of patients		Effect		Quality (Certainty)	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No Vaccination with Nuvaxovid**	**No vaccination with Placebo**	**Vaccine efficacy (VE) or risk ratio (RR)(95% CI)**	**Absolute**		
Efficacy of Nuvaxovid against COVID-19 (milde, moderate, severe)												
2	Randomised trials	Serious study limitations[1]	no serious inconsistency	very serious[2,3]	no serious imprecision	none	Cumulative events: Study 301: 14/17.312 0,08% Study 302: 10/7.020 0,07%	Cumulative events: Study 301: 63/8.140 0,8% Study 302: 96/7.019 0,68%	Pooled RR under random effects model: 0.10 [0.07, 0.16] VE: 90% (84 to 93)	Absolute risk in placebo group: 10 per 1000 Absolute risk in intervention group: 1 per 1000 (from 0 to 2)	⊕ VERY LOW	IMPORTANT
Efficacy of Nuvaxovid against COVID-19 (severe)												
2	Randomised trials	Serious study limitations[1]	no serious inconsistency	very serious[2,3]	serious[4]	none	Cumulative events: Study 301: 0/17.312	Cumulative events: Study 301: 4/8.140	Pooled RR under random	Absolute risk in placebo	⊕ VERY LOW	IMPORTANT

							0% Study 302: 0/7.020 0%	0,05% Study 302: 5/7.019 0,04%	effects model: 0.07 [0.01, 0.54] VE: 93% (46 to 99)	group: <1 per 1000 Absolute risk in intervention group: <1 per 1000 (from 0 to 1)		
Efficacy of Nuvaxovid against COVID-19 (Infection)												
2	Randomised trials	No data	No data	No data	No data	No data	Cumulative events:	Cumulative events:	No data	Calculation based on published data not possible		IMPORTANT
Efficacy of Nuvaxovid against COVID-19 hospitalisation												
2	Randomised trials	Serious study limitations[1]	No data	very serious[2,3]	very serious[5]	No data	302: 0 cases (PP-Group)	302: 1 case (PP-Group)	RR: 0.33 [0.01 to 8.18] VE: 67% (0 to 99)	Absolute risk for placebo group: <1 per 1000 Absolute risk for intervention group: <1 per 1000 (0 to 8)	⊕ VERY LOW	CRITICAL
Efficacy of Nuvaxovid against ICU												
2	Randomised trials		No data	No data	No data	No data	No data	No data	No data	Calculation based on published data not possible		CRITICAL
Efficacy of Nuvaxovid against Beatmung												
2	Randomised trials		No data	No data	No data	No data	No data	No data	No data	Calculation based on published data not possible		CRITICAL

Efficacy of Nuvaxovid against Death												
2	Randomised trials		No data	No data	No data	No data	No data	No data	No data	Calculation based on published data not possible		CRITICAL
Local reaction (any local AE) after dose 2												
1	Randomised trial[6]	Some concerns	no serious inconsistency	serious[2]	no serious imprecision	none	301: 78,9%	301: 21,7%	RR based on 301: 3.64 [3.49 to 3.79]	Absolute risk with placebo: 217 per 1000 Absolute risk with intervention: 790 per 1000 (758 to 823)	⊕⊕⊕ MODERATE	IMPORTANT
Systemic reaction (any systemic AE) after dose 2												
1	Randomised trial[6]	Some concerns	no serious inconsistency	serious[2]	no serious imprecision	none	301: 70%	301: 36%	RR based on 301: 1.94 [1.88 to 2.00]	Absolute risk with placebo: 359 per 1000 Absolute risk with intervention: 696 per 1000 (674 to 717)	⊕⊕⊕ MODERATE	IMPORTANT
Serious adverse event (SAE)												
2	Randomised trials	Serious study limitations[7]	no serious inconsistency	serious[2]	serious[8]	none	Study 301: 169/19.729 (0,9%) Study 302: 44/7.7.569 (0,6%)	Study 301: 94/ 9.853 (1,0%) Study 302: 44/7.570 (0,6%)	Pooled RR under random effects model: 0.92 [0.75, 1.15]	Absolute risk in placebo group: 8 per 1000 Absolute risk in intervention group: 7 per 1000 (6 to 9)	⊕ VERY LOW	CRITICAL

Adverse event of special interest (PIMMC)												
2	Randomised trials	serious study limitations[7]	no serious inconsistency	Serious[2]	Serious[8]	none	Study 301: 16/19.729 (0,08%) Study 302: 5/7.569 (0,07%)	Study 301: 3/9.853 (0,03%) Study 302: 7/7.570 (0,09%)	Pooled RR under random effects model: 1.35 [0.37, 4.95]	Absolute risk in placebo group: <1 per 1000 Absolute risk in intervention group: <1 per 1000 (0 to 3)	⊕ VERY LOW	CRITICAL
Adverse event of special interest (COVID-related)												
2	Randomised trials	serious study limitations[7]	no serious inconsistency	Serious[2]	Serious[8]	none	Study 301: 4/19.729 (0,02%) Study 302: 8/7.569 (0,1%)	Study 301: 7/9.853 (0,04%) Study 302: 22/7.570 (0,3%)	Pooled RR under random effects model: 0.34 [0.17 , 0.67]	Absolute risk in placebo group: 2 per 1000 Absolute risk in intervention group: <1 per 1000 (0 to 1)	⊕ VERY LOW	CRITICAL

[1] both studies were rated with a high risk of bias for this outcome.

[2] In the 302-Trial, approximately 28% of the trial participants (vaccine arm: n=1.953) were 65 years of age or older. Overall vaccine efficacy against symptomatic disease was 88.9% (95% CI, 12.8 to 98.6). While supportive evidence (immunogenicity data in this age group) suggest that the vaccine elicits an immune response comparable to younger adults, the evidence was downgraded for imprecision due to large confidence intervals and the limited sample size. 301-Trial not adequately powered to assess vaccine efficacy in the age group 65 and older.

[3] No information about efficacy against currently circulating Variants of Concern or Variants of Interest, especially Delta and Omicron

[4] serious imprecision due to very few observed events, resulting in a wide confidence interval.

[5] Imprecision due to the very low lower value of the confidence interval, which as a true value would not lead to recommendation.

[6] The effects here were only presented for one randomised trial, as for the other study the population in the two study arms have been not adequately presented (79,6% versus 16,4% for local events and 64% and 30% for systemic events in study 302)

[7] one study was rated with a high risk of bias and the other study with some concerns for bias for this outcome.

[8] Serious imprecision because of confidence interval including both, a potential benefit and harm for the intervention.