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Risk of Appendicitis After mRNA COVID-19 Vaccination in a Danish Population

Appendicitis has been reported as a potential adverse event after immunization with mRNA-based COVID-19 vaccines, based on trial data,[1] adverse event report data,[2] and observational data.[3] We evaluated the risk of appendicitis after receiving an mRNA COVID-19 vaccination and after diagnosis of SARS-CoV-2 infection compared with the risk of appendicitis in unvaccinated individuals.

Methods | In this cohort study, we used Danish nationwide registers to identify recipients of the BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine and all individuals aged 12 years and older with SARS-CoV-2 confirmed by polymerase chain reaction (PCR) test from December 27, 2020, to November 30, 2021. For comparison, we analyzed an unvaccinated reference group of Danish individuals aged 12 years and older tested for SARS-CoV-2 infection (89% of Danish population aged 12 years and older) until November 30, 2021, by assigning each individual a random index date between January 1 and June 30, 2021. Weighting was then applied to adjust for potential confounders. By law, registry-based studies are exempt from ethical review and informed consent in Denmark. The study followed the STROBE reporting guideline.

We excluded individuals with a previous appendicitis or appendectomy, individuals immunized with non-mRNA COVID-19 vaccines, and individuals with PCR-confirmed SARS-CoV-2 before study inclusion.

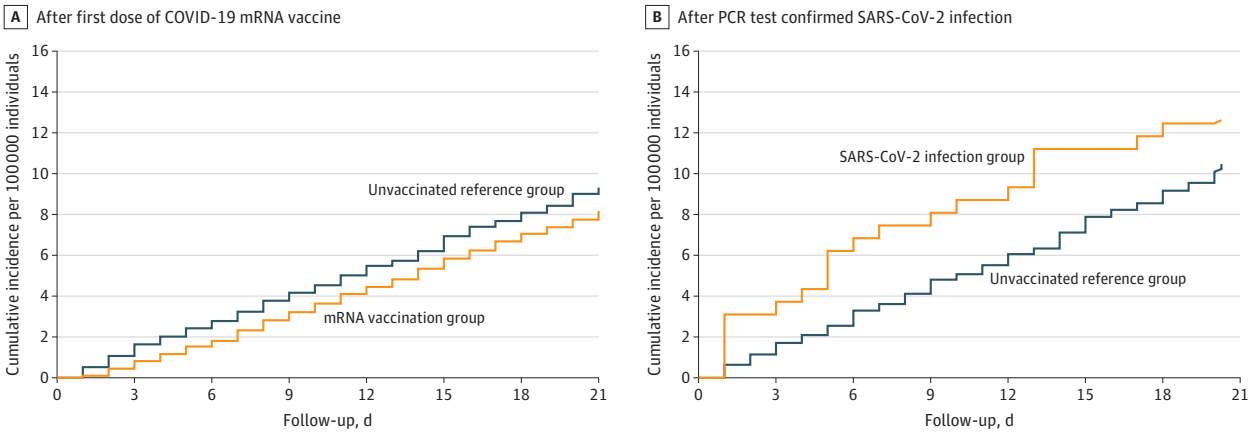
The main exposures were first doses of the BNT162b2 or mRNA-1273 vaccine, which were evaluated as a combined exposure and separately for each vaccine. We evaluated the risk of study outcomes after the second vaccine dose or SARS-CoV-2 infection. The main outcome was a composite of a first-ever hospital contact with an appendicitis or appendectomy diagnosis code. Individuals were followed up for 21 days after inclusion (entry date included) and were censored at the end of the follow-up period, occurrence of the outcome, death, or SARS-CoV-2 infection. Individuals in the unvaccinated and SARS-CoV-2 infected groups were further censored if immunized against COVID-19 during follow-up.

We constructed cumulative incidence curves and obtained risk ratios and risk differences (per 100 000 individuals). Estimates were adjusted for age, sex, municipality, immigration status, history of inflammatory bowel disease, diabetes, and the number of antibiotic prescription fills during the past 2 years using propensity score–derived standardized morbidity ratio weights.

Results | Among 4 048 883 individuals immunized with mRNA COVID-19 vaccines, 330 episodes of appendicitis occurred within 21 days of the first dose, corresponding with 8.1 episodes per 100 000 individuals vaccinated (**Figure**). The rate after the second dose was 8.6 per 100 000 individuals (340 cases among 3 944 408 individuals). Compared with the unvaccinated reference group, we found no increased risk of appendicitis after mRNA COVID-19 vaccination, with an adjusted risk ratio of 0.93 (95% CI, 0.79-1.11) after the first dose and 0.99 (95% CI, 0.84-1.18) after the second dose. This null association was stable across age groups, sexes, and vaccine types (**Table**). In analyses of the risk of appendicitis after SARS-CoV-2 infection vs the unvaccinated reference group, the adjusted risk ratio was 1.25 (95% CI, 0.79-1.99).

Discussion | In this nationwide study comprising 4 million vaccinated individuals, we found no association between immunization with mRNA-based COVID-19 vaccines and appendicitis. The safety signal was raised when BNT162b2 vaccine trials showed higher numbers of appendicitis cases in vaccinated than placebo groups; the US Food and Drug Administration then listed appendicitis as an adverse effect of special interest.[1,4] This suspicion was backed by disproportional reporting of adverse events[2] and an Israeli cohort study estimating an excess risk of appendicitis of 5.0 episodes per 100 000 individuals after vaccination.[3] However, an interim analysis of US surveillance data found no association.[5] Limitations of the study include the nonrandomized observational design,

Figure. The 21-Day Cumulative Incidence of Appendicitis or Appendectomy



PCR indicates polymerase chain reaction.

Table. Risk of Appendicitis or Appendectomy After mRNA COVID-19 Vaccination and SARS-CoV-2 Infection[a]

	No./total No. of individuals		Adjusted risk ratio (95% CI)[b]	Adjusted risk difference, events per 100 000 individuals (95% CI)[b]
	Exposure group	Weighted reference group		
First dose of mRNA vaccine				
All	330/4 048 883	350/4 010 544	0.93 (0.79 to 1.11)	−0.58 (−2.01 to 0.86)
Median age (IQR), y	50 (31-66)	49 (32-62)	NA	NA
Age, y				
12-24	75/689 085	83/689 131	0.90 (0.66 to 1.24)	−1.14 (−4.73 to 2.44)
25-44	81/1 000 720	110/1 000 810	0.74 (0.55 to 0.98)	−2.91 (−5.66 to −0.15)
≥45	174/2 359 078	160/2 341 472	1.08 (0.82 to 1.43)	0.56 (−1.39 to 2.52)
Sex				
Female	182/2 032 326	176/2 008 745	1.02 (0.81 to 1.29)	0.20 (−1.84 to 2.25)
Male	148/2 016 557	174/2 001 570	0.85 (0.66 to 1.08)	−1.33 (−3.33 to 0.67)
Vaccine type				
BNT162b2	294/3 531 437	309/3 494 939	0.94 (0.79 to 1.12)	−0.53 (−2.04 to 0.99)
mRNA-1273	36/517 446	41/518 456	0.87 (0.61 to 1.25)	−1.01 (−3.58 to 1.55)
Second dose of mRNA vaccine				
All	340/3 944 408	339/3 904 552	0.99 (0.84 to 1.18)	−0.06 (−1.52 to 1.41)
Median age (IQR), y	51 (32-66)	49 (33-63)	NA	NA
Age, y				
12-24	87/645 253	77/645 306	1.13 (0.83 to 1.52)	1.50 (−2.35 to 5.35)
25-44	96/956 771	106/956 903	0.91 (0.69 to 1.20)	−1.00 (−3.92 to 1.92)
≥45	157/2 342 384	158/2 324 800	0.99 (0.74 to 1.31)	−0.10 (−2.04 to 1.83)
Sex				
Female	174/1 980 903	170/1 956 427	1.01 (0.80 to 1.28)	0.11 (−1.96 to 2.17)
Male	166/1 963 505	168/1 947 935	0.98 (0.77 to 1.25)	−0.19 (−2.27 to 1.88)
Vaccine type				
BNT162b2	297/3 443 474	300/3 405 546	0.98 (0.82 to 1.17)	−0.18 (−1.72 to 1.36)
mRNA-1273	43/500 934	40/501 887	1.08 (0.78 to 1.51)	0.66 (−2.17 to 3.48)
SARS-CoV-2 infection[c]				
All	20/159 115	16/159 241	1.25 (0.79 to 1.99)	2.53 (−3.20 to 8.25)
Median age (IQR), y	31 (21-46)	32 (22-46)	NA	NA
Sex				
Female	9/78 694	9/78 749	1.04 (0.52 to 2.07)	0.45 (−7.39 to 8.29)
Male	11/80 421	7/80 493	1.49 (0.79 to 2.81)	4.51 (−3.83 to 13)

Abbreviation: NA, not applicable.

[a] Risk of appendicitis or appendectomy 21 days after immunization with the first or second dose of the BNT162b2 or mRNA-1273 vaccine and 21 days after SARS-CoV-2 infection confirmed with polymerase chain reaction test compared with an unvaccinated reference group.

[b] Risk estimates were obtained using binomial regression with adjustment for age, sex, municipality, immigration status, history of inflammatory bowel disease, diabetes, and number of antibiotic prescription fills during the past 2 years using standardized morbidity ratio weighing.

[c] Age stratification was omitted because of the low number of events.

accuracy of register-based identification of appendicitis,[6] and inability to detect possible risks beyond the predefined risk interval. Further studies from different settings will be needed to fully eliminate appendicitis as an mRNA COVID-19 vaccination safety concern.

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COMMENT & RESPONSE

Management of Chronic Low Back Pain

To the Editor We read Dr Cohen's Evidence to Practice[1] with great interest. The review provides an excellent evidence-supported overview of approaches to management for chronic low back pain (CLBP). We share the author's sentiment that evidence-supported, active, multidisciplinary treatment strategies to manage CLBP with better patient engagement and shared decision-making tend to be underused, and passive treatments for which the evidence is lacking tend to be overused. We applaud the author for rightly pointing out system factors (eg, misaligned fee-for-service reimbursement models that reward procedure-based care), barriers (eg, limited access and higher out-of-pocket costs for active treatments, eg, yoga/exercise therapy), and cultural factors (eg, patient values/preferences for pain relief) that "deter utilization" of effective treatment interventions.

Although CLBP procedure-based care is emphasized by some physiatrists and pain specialists, the American Academy of Physical Medicine & Rehabilitation (AAPM&R), the world's largest organization of physiatrists, advocates for evidence-based practice as reflected in its vision statement.[2] In the future envisioned by AAPM&R, all payers, regulators, hospital systems, and the public will value a holistic philosophy that will optimize function and minimize disability through an evidence-based collaborative approach to providing timely and appropriate care.

Physiatrists' patient-centered, culturally competent, comprehensive, multidisciplinary approach can, and has, filled the need that Dr Cohen called on for "sophisticated care coordination" between primary care and specialty care. Physiatrists regularly direct patients through the complexities of our current health care system toward affordable, accessible, and effective care. There is evidence to support this claim. Fox and colleagues reported that requiring a consultation with physical medicine and rehabilitation prior to surgical referral for lower back pain decreased the surgical rate and its associated costs by 25%, and 74% of patients were satisfied or very satisfied with the consultation.[3] An analysis of a Medicare Limited Data Set (5% sample) of 170 patients seen by a primary care practitioner for lower back pain found that the average 2-year spine-specific per-member per-month spending was $3978 for the cohort referred to physiatrists vs $7387 for the cohort referred to spine surgeons.[4]

In conclusion, we agree that better use of evidence-based therapies for CLBP management is needed to drive long-term improvement in outcomes. Physiatrists can be valuable partners for primary care practitioners providing this care. A broad paradigm shift to a value-based system of care will not be simple, but AAPM&R will continue to advocate for better access, and for physiatrists to provide the most comprehensive evidence-based care available to effectively treat patients with CLBP.