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ORIGINAL RESEARCH

Longevity of Immunoglobulin-G Antibody Response Against Nucleocapsid Protein Against SARS-CoV-2 Among Healthcare Workers

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Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the latest pandemic and the most significant challenge in public health worldwide. Studying the longevity of naturally developed antibodies is highly important clinically and epidemiologically. This paper assesses the longevity of antibodies developed against nucleocapsid protein amongst our health-care workers.

Methods: This longitudinal cohort study was conducted at a tertiary hospital, Saudi Arabia. Anti-SARSsCoV-2 antibodies were tested among health-care workers at three-point intervals (baseline, eight weeks, and 16 weeks).

Results: Of the 648 participants, 112 (17.2%) tested positive for Coronavirus (COVID-19) by PCR before the study. Of all participants, 87 (13.4%) tested positive for anti-SARS-CoV-2 antibodies, including 17 (2.6%) participants who never tested positive for COVID-19 using rt-PCR. Out of the 87 positive IgG participants at baseline, only 12 (13.7%) had remained positive for anti-SARS-CoV-2 antibodies by the end of the study. The IgG titer showed a significant reduction in values over time, where the median time for the confirmed positive rt-PCR subgroup from infection to the last positive antibody test was 70 (95% CI: 33.4–106.5) days.

Conclusion: Health-care workers are at high risk of exposure to the SARS-CoV-2 virus, and contracting an asymptomatic infection is not unlikely. Developing and sustaining natural immunity differs from one person to another, while the rate of positive IgG anti-SARS-CoV-2 wanes over time.

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Keywords: antibodies, longevity, COVID-19, SARS-CoV-2, healthcare workers, HCW

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease-2019 (COVID-19) and its rapid spread worldwide, causing a global pandemic since December 2019. As of May 2022, more than 520 million people were infected with SARS-CoV-2, and more than 6 million associated deaths were reported worldwide.[1]

Humans are exposed to different kinds of viruses constantly, and their responses to these infections differ from one individual to another.[2] This response depends on each individual's immune system: the innate immune system and the

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adaptive immune system.[3] The development of antibodies from a previous infection or vaccination, and having adequate memory cells, are essential for long-term immune protection.[4,5]

SARS-CoV-2 has many encoded proteins, and serological assays for SARS-CoV-2 utilize two structural proteins for characterizing immune response to infection.[6] These proteins are the structural spike protein (S) and the nucleocapsid protein (N).[6] It is assumed that immunity produced post-infection will last up to one year, and one study showed that antibody response might last 500 days depending on the clinical severity of the disease as well as the patient's characteristics.[7] Antibodies develop within 2 to 3 weeks after infection with the SARS-CoV-2 virus, and the antibodies are targeted against the nucleocapsid protein as well as the receptor-binding domain (RBD), the S1 and S2 domains of the spike glycoprotein.[6,8]

One study of health-care workers (HCWs) showed that anti-spike IgG antibodies remained positive in 94% at 180 days.[9] In this study, we assess the longevity of antibodies developed against the nucleocapsid protein among HCWs with periodic serology testing for up to four months.

Methods

Study Design

This longitudinal cohort study was conducted at a tertiary hospital, Saudi Arabia.[10] The study aimed to assess the immune status and positive seroconversion prevalence against SARS-CoV-2 amongst HCWs. This study was registered as a clinical trial at ClinicalTrials.gov with the Identifier of NCT04469647.[21]

Participants were invited to participate in this study via a staff announcement email sent to all employees. All participants who presented without COVID-19 symptoms were enrolled in the study, and followed up for four months. Staff members with COVID-19-like symptoms such as fever, runny nose, or cough were excluded from the study. A serology blood test was performed at enrollment (baseline), eight weeks, and 16 weeks. A database of all participants' data with their study ID numbers was created for the questionnaire, visit date, and test results. When their follow-up test was due, all participants received a reminder email.

The study received the approval of Johns Hopkins Aramco Healthcare Institutional Review Board (IRB # 20-09). Each participant was assigned a study ID, and written informed consent was obtained at enrollment. Participants who tested positive for antibodies against SARS-CoV-2 at baseline were asked to repeat the test at 8 and 16 weeks.

Data Collection

A 10 mL blood sample was collected from participants by a phlebotomist at the local hospital laboratory at every round of testing. The SARS-CoV-2 IgG assay results were then sent to the research team as positive or negative, and their titer index was entered into the study database. Two nurses entered all completed questionnaires into the study database and validated them by the study's principal investigator.

Testing Method

The Architect i2000SR system and the SARS-CoV-2 nucleocapsid antigen were used to determine an automated, two-step immunoassay for the qualitative detection of IgG antibodies against the N-protein of SARS-CoV-2 in human serum using chemiluminescent microparticle immunoassay (CMIA) technology. The index was interpreted as positive (reactive) if it was equivalent to or above 1.4 and negative (non-reactive) if it was below 1.4. Though not a direct titer, higher index values highly correlate to neutralization titers.

Data Analysis

Data were entered and analyzed using the statistical package IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. Categorical data were presented by frequencies and percentages. Binary logistic regression was used to assess the factors associated with the positive IgG at eight weeks. The generalized linear model was used to compare the rate of positive IgG across the study period and COVID-19 status. Moreover, JMP from SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) was used to test the association between IgG status categories (yes/no), and the factors of interest were assessed using the Chi-square test, Fisher's exact test, as appropriate. The difference in titer level across

follow-ups was assessed using ANOVA of repeated measures with a Greenhouse-Geisser correction and the Wilcoxon signed-rank test. The longevity of positive IgG was computed from the date of diagnosis of COVID-19 by PCR to the date of the last positive antibody test during follow-up. The Kaplan–Meier (KM) method was used to estimate the median time to the last positive IgG test. Associations and hazard ratios (HR) for factors of interest were assessed using the Cox proportional hazards regression model. Multivariate analysis was conducted using Cox regression with the forward-enter method to determine contributing factors that had an independent impact. A test was considered significant if the p-value is <0.05.

Results

More than half of the participants were females (53.2%) and non-Saudis (61.7%). The vast majority of the participants were above 30 years of age (89.8%) and were non-smokers (86.9%). Of the participants, 29.3% were nurses, 28.6% were physicians, and 25.2% were non-clinicians (Table 1).

Table 1 Participants' Baseline Characteristics

		N	%
Gender	Male	303	46.8%
	Female	345	53.2%
Age (years)	21–30	66	10.2%
	31–40	188	29.1%
	41–50	200	30.9%
	51+	193	29.8%
Nationality	Saudi	235	38.3%
	Non-Saudi	379	61.7%
Smoker	No	551	86.9%
	Yes	83	13.1%
Occupation in Healthcare facility	Physician	178	28.6%
	Nurse	182	29.3%
	Other Clinician	105	16.9%
	Non-Clinician	157	25.2%
Years of Experience	0–5	97	19.5%
	6–10	83	16.7%
	11–15	72	14.5%
	16–20	79	15.9%
	21–25	75	15.1%
	26+	91	18.3%
Have you been diagnosed with COVID-19 before?	Yes	112	17.2%
	No	491	75.8%
	Unknown	45	7%

A total of 648 have done the baseline serology test, and only 87 (13.4%) have developed anti-SARS-CoV-2 antibodies. Of these 87 participants, 17 (2.6%) never tested positive for SARS-CoV-2 by rt-PCR. At the first follow-up test – at eight weeks, 436 (67.3%) participants completed the serology test, and 43 (9.8%) tested positive for anti-SARS-CoV-2 antibodies. Out of those 43, 10 participants tested positive for anti-SARS-CoV-2 antibodies after their negative baseline result. Finally, 38 (5.9%) completed the final follow-up serology test, and only 18 (47.3%) tested positive for anti-SARS-CoV-2 antibodies. Out of the 87 positive IgG participants at baseline, only 12 (13.7%) had remained positive for anti-SARS-CoV-2 antibodies by the end of the study at 16 weeks.

Moreover, 112 (17.2%) reported testing positive for COVID-19 by rt-PCR. Participants with positive rt-PCR for SARS-CoV-2 reported experiencing fatigue (66.3%), headache (66%), muscle aches (64.2%), cough (54.3%), general malaise (51.1%), fever (48.3%), sore throat (46.7%), joint ache (46.2%), loss of appetite (45.3%), or chills (45.2%). Additionally, 21.4% of these participants suffered from obesity, 11.2% had diabetes, and 6.3% had asthma.

Participants who were diagnosed with COVID-19 by rt-PCR had a significantly higher chance of positive IgG on their first serology test post infection [OR = 27.57; p-value <0.001; 95% CI=(15.07–50.44)]. Moreover, we assessed the association between having positive SARS-CoV-2 antibodies – at baseline – with demographic variables, symptoms, and comorbidities. Participants were likely to test positive for IgG against SARS-CoV-2 if they were nurses (41% vs 27.5%) P-value 0.01, did not visit their families (56.5% vs 48%) P-value 0.03, tested positive COVID-19 rt-PCR (79% versus 9.2%) P-value <0.001, and if they were exposed to a known COVID-19 patient (44.4% versus 17.3%) P-value <0.001. Symptoms were significantly associated with testing positive for IgG (*P*-value <0.001) in a univariate (Table 2); however, there was no association between IgG status and comorbidities.

Table 2 Univariate Analysis of the Association Between Immunity Status and Reported Symptoms at Baseline

Symptoms	Positive IgG		Total
	No =561	Yes =87	
Have you experienced any respiratory symptoms?*	131 (24.7%)	51 (64.6%)	182 (29.8%)
Fever (≥37.8 °C)	32 (9.8%)	36 (60%)	68 (17.6%)
Sore throat*	83 (20.9%)	31 (44.9%)	114 (24.5%)
Runny Nose*	60 (15.3%)	26 (37.7%)	86 (18.7%)
Cough*	58 (14.8%)	38 (55%)	96 (20.8%)
Shortness of Breath*	38 (9.6%)	22 (31%)	60 (12.8%)
Chills*	30 (7.5%)	32 (45.7%)	62 (13.4%)
Vomiting*	9 (2.3%)	9 (12.9%)	18 (3.9%)
Nausea*	23 (5.8%)	21 (39.6%)	44 (9.5%)
Diarrhea*	44 (11%)	25 (34.2%)	69 (14.6%)
Headache*	72 (18%)	44 (60.3%)	116 (24.5%)
Rash*	6 (1.5%)	5 (7.4%)	11 (2.4%)
Conjunctivitis*	10 (2.5%)	4 (6.2%)	14 (3%)
Muscle aches*	49 (12.3%)	47 (67%)	96 (20.6%)
Joint ache*	29 (7.4%)	33 (47.8%)	62 (13.4%)
Loss of appetite*	30 (7.6%)	33 (47%)	63 (13.5%)

(*Continued*)

Table 2 (Continued).

Symptoms	Positive IgG		Total
	No =561	Yes =87	
Nose bleed*	3 (0.8%)	4 (5.9%)	7 (1.5%)
Fatigue*	57 (14.3%)	47 (65.3%)	104 (22%)
General malaise*	42 (10.6%)	34 (50%)	76 (16.4%)

Notes: Chi-square independent test and/or Fisher's exact test were used where appropriate. *Significant association at a level of 0.001.

Table 3 Factors Associated with the Positive IgG at Eight Weeks

		P-value	OR	95% C.I.for OR	
				Lower	Upper
Diagnosed with COVID-19 by rtPCR	Yes	<0.001	40.94	18.58	90.22
	No(ref)		1.00		
Gender	Male	0.043	2.50	1.03	6.07
	Female(ref)		1.00		
Age(years)	21–30	0.156	0.24	0.03	1.72
	31–40	0.189	0.37	0.08	1.64
	41–50	0.506	1.46	0.48	4.44
	51+(ref)		1.00		
Nationality	Saudi	0.463	1.40	0.57	3.41
	Non-Saudi(ref)				
Smoker	No	0.548	1.43	0.44	4.64
	Yes(ref)		1.00		
Occupation in Healthcare facility	Physician	0.044	0.27	0.07	0.96
	Nurse	0.754	1.20	0.39	3.69
	Other Clinician	0.625	0.74	0.22	2.47
	Non-Clinician(ref)		1.00		
Years of Experience	0–5	0.510	1.86	0.30	11.68
	6–10	0.912	0.91	0.15	5.35
	11–15	0.774	1.29	0.23	7.10
	16–20	0.499	0.60	0.14	2.64
	21–25	0.685	1.34	0.33	5.47
	26+(ref)		1.00		

Table 3 presents factors associated with IgG positivity at eight weeks. Only gender, occupation, and previous diagnosis of COVID-19 had a significant association with positive IgG status at the first follow-up test. Males had higher chance of positive IgG as compared to female [OR = 2.5; p-value=0.43; 95% CI=(1.03–6.07)], physicians also had

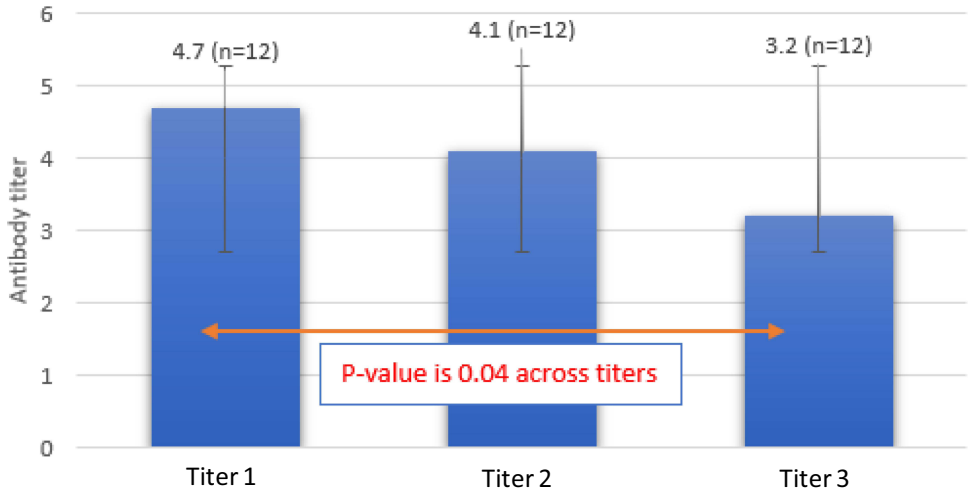

Figure 1 Significant trend for decreasing titer value throughout the study period. P value was estimated using ANOVA.

a slightly higher chance of positive IgG [OR = 0.27; p-value=0.44; 95% CI=(0.07–0.96)], and previous diagnosis of COVID-19 had higher chance of positive IgG [OR = 40.94; p-value <0.001; 95% CI=(18.58–90.22)] (Table 2).

When titers were compared using ANOVA of repeated measures test (n = 12), there is an overall significant (F = 3.8, P-value = 0.04) trend for decreasing of IgG titer over time (4.7, 4.1, 3.2) at baseline, eight weeks and 16 weeks for those who remain positive from start until the end of follow-up (Figure 1). Moreover, for the cohort of 87 participants who tested positive for antibodies against SARS-Cov-2, we analyzed the difference in IgG using pairwise comparisons, as shown in Table 4.

The longevity of IgG positivity was estimated using the Kaplan–Meier curve. The median time for the confirmed positive rt-PCR subgroup from infection to the last positive antibody test was 70 days, with a 95% CI of 33.4–106.5 (Figure 2). Moreover, all symptoms were entered into a Cox regression model to assess which symptoms contribute to a longer duration of antibody positivity. The model showed that fever (HR = 2.9, 95% CI: 1.1–7.8), chills (HR = 2.5, 95% CI 1.05–5.9), and vomiting (HR = 5.2, 95% CI: 1.2–23.2) were significantly associated factors with longer duration of immunity (Table 5).

Discussion

The development of antibodies against new pathogens post-infection is a common phenomenon to provide the human body with immunity and protection from that particular virus. Antibodies against SARS-CoV-2 can be detected as early as two weeks from the onset of the symptoms depending on the patient's immune system.[11]

Table 4 Pairwise Comparisons of the Titer Levels

		Mean	N*	Std. Dev	t Statistics	P-value
Pair 1	IgG at baseline	5.1	34	1.74	9.38	<0.001
	IgG at 8 weeks	3.4	34	1.74		
Pair 2	IgG at 8 weeks	4.43	12	2.1	3.91	<0.001
	IgG at 16 weeks	3.2	12	1.61		

Note: P-value estimated by Wilcoxon signed-rank test. Titer 1 is the baseline and calculated at the beginning of the study, titer 2 is calculated at eight 8 weeks, and titer 3 is calculated at 16 weeks. Pair 1 is a comparison between baseline and eight weeks, and Pair 2 is a comparison between eight and 16 weeks results. *The same subjects who were positive on each test.

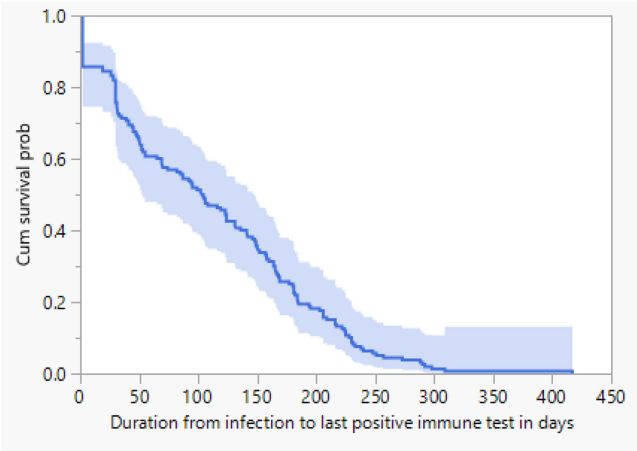

Figure 2 Kaplan–Meier curve to estimate the longevity of positive IgG results.

In this study, of 648 HCWs, only 87 (13.4%) tested positive for anti-SARS-CoV-2 antibodies. The positivity rate of HCWs to anti-SARS-CoV-2 antibodies is a function of the testing time and the infection rate in both the community and the health-care settings. In a previous study from Saudi Arabia, the rate of positivity was 2.36%, and the rate was higher in the case-hospital (2.9%) compared to the control group (0.8%) (P-value <0.001).[12] That study was done earlier in the

Table 5 Multivariate Cox Regression Model of Symptoms versus Immunity Status

	B	SE	HR	95.0% CI for HR		Sig.
				Lower	Upper	
Fever Over 37*	1.09	0.49	2.98	1.14	7.81	0.03
Sore Throat	−0.35	0.49	0.70	0.27	1.82	0.47
Cough	0.44	0.41	1.55	0.70	3.46	0.28
Runny Nose	0.88	0.51	2.40	0.88	6.57	0.09
Shortness of Breath	−0.23	0.44	0.79	0.34	1.87	0.59
Chills*	0.92	0.44	2.51	1.06	5.95	0.04
Vomiting*	1.66	0.76	5.27	1.19	23.29	0.03
Nausea	−1.16	0.62	0.31	0.09	1.06	0.06
Diarrhea	−0.33	0.44	0.72	0.30	1.72	0.46
Headache	−1.14	0.61	0.32	0.10	1.05	0.06
Rash	−1.58	0.85	0.21	0.04	1.09	0.06
Conjunct	1.55	0.82	4.72	0.94	23.62	0.06
Muscle Ache	0.20	0.57	1.22	0.40	3.71	0.73
Joint Ache	−0.03	0.57	0.97	0.32	2.98	0.96
Loss of Appetite	0.45	0.44	1.58	0.67	3.73	0.30
Nose bleed	0.55	0.73	1.73	0.41	7.27	0.46
Fatigue	−0.32	0.58	0.72	0.23	2.28	0.58
General Malaise	0.24	0.53	1.27	0.45	3.60	0.65

Note: *Significant association at a level of 0.001.

pandemic than the current one. In another study, 223 of 693 (32.2%) were seropositive for SARS-CoV-2 antibodies, and among those, 197 (88.3%) had never been diagnosed with COVID-19.[13] On the other hand, we also found that of the 87 positives for anti-SARS-CoV-2 antibodies, 17 (2.6%) never tested positive for SARS-CoV-2 by rt-PCR. Those who never tested positive for COVID-19 using an rt-PCR may have had asymptomatic infection with SARS-CoV-2.[14,15] In a systematic review, the rate of asymptomatic SARS-CoV-2 infection was 19% (95% (CI) 15–25%).[16]

Another similar yet larger study was conducted in Riyadh, Saudi Arabia. The institution where the study was conducted had almost twice the staff number and three times our sample size.[17] However, the rate of seroprevalence was slightly lower with (10.8%) compared to our seroprevalence rate of (13.4%). The discrepancy can be due to the differences in the sensitivity, specificity, and design of the assays used as well as the study populations. More to that, participants may have had positive IgG or did not mount an IgG by the time they performed the test. The highest seroprevalence rate group in their study was amongst respiratory therapists while our nurses had the highest rate, both can be explained by being frontliner and in direct contact with infected patients.

Several (17 participants) HCWs with no prior history of COVID-19 disease had positive anti-SARS-CoV −2 antibodies. However, the positivity rate was higher over time among those who had positive rt-PCR than those who did not. The positivity rate was 30.4% vs 1.8% at six months for those who were rt-PCR positive and negative, respectively. The immune response had been variable among those with COVID-19, depending on the severity of the disease. In a study from Bangladesh, the rate of positive serology was 100% and 45% at day 30 after infection in symptomatic and asymptomatic, respectively.[18] An additional study found that among outpatient and asymptomatic individuals, anti-SARS-CoV-2 antibodies decreased over five months after infection.[19]

We found that the longevity of the antibodies was associated with fever (HR = 2.9, 95% CI: 1.1–7.8), chills (HR = 2.5, 95% CI 1.05–5.9), and vomiting (HR = 5.2, 95% CI: 1.2–23.2). One study showed that neutralizing antibodies declined over time, which was associated with age <50 years, mild disease, comorbidities, obesity, and being male.[20]

One of the main limitations in this study was the decreasing number of participants at each follow-up point. This could be due to participants receiving their first dose of the SARS-CoV-2 vaccine and feeling at ease knowing they most likely developed immunity against the virus. Another limitation is the relatively small sample size, and certainly having a larger sample size would strengthen the study. Another area of limitation is related to the sensitivity and specificity of the laboratory test that had been used to detect antibodies and the occurrence of false-positive and false-negative tests should be taken into consideration. The study had only tested for IgG with no specific test to measure the exact titers and thus waning immunity overtime should also be considered. The representation of this study of all HCWs may not be generalized as initially HCWs who volunteered in the study may have particular reasons to participate in the study such as documenting positive serology prior to the vaccine availability.

Moreover, the infection rate across the community is most likely to change with time, making the prevalence dynamic. Thus, the intention of this study was to estimate the seroprevalence at the beginning of the pandemic rather than monitoring its progression for longer period and over the course of the pandemic. It was clearly observed in this study that immunity wanes down with an average time of 70 days. This raises a question for future study of the longevity of antibodies developed post vaccination against SARS-CoV-2.

Conclusion

In conclusion, the rate of positive IgG anti-SARS-CoV-2 for the N-antigen protein wanes down over time and is not a long-lasting response. This observation is similar to previous observations indicating that this test could not be used solely as a seroprevalence tool.[19] However, Chaudhry et al suggested in their study that testing negative against the N-protein does not necessarily mean an absolute lack of immunity as patients may produce antibodies against the S-protein antigen, which would help neutralize the SARS-CoV-2 virus.[6] Thus, extensive follow-up studies are needed to establish correlates of protection against reinfection and/or disease and the duration of antibody-mediated protection. Although, as of the time of writing this paper, more than 61% of the population worldwide and more than 70% of the Saudi Arabian population have been fully vaccinated, and longevity studies of antibodies produced against SARS-CoV-2 post-vaccination are highly recommended.

Data Sharing Statement

Datasets including demographical data, serology testing results and questionnaire responses can be provided upon request from Dr. Hayat Mushcab. The encrypted dataset can be uploaded to the system and shared with the reviewers accordingly.

Ethics

The study adheres to the Declaration of Helsinki and has received the Institutional Review Board's approval (IRB # 20-09) on the 13th of May 2020.

Informed Consent

Each participant was assigned a study ID, written informed consent, and a hard copy of the WHO's risk factors assessment questionnaire.

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Author Contributions

All authors contributed significantly to work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. They took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

All authors declare that there is no competing financial interest directly or indirectly in this work.

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