Supplementary Appendix

Supplement to: Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Effect of mRNA vaccine boosters against SARS-CoV-2 omicron infection in Qatar. N Engl J Med. DOI: 10.1056/NEJMoa2200797

This appendix has been provided by the authors to give readers additional information about the work.

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Section S1. Laboratory methods

Nasopharyngeal and/or oropharyngeal swabs were collected for PCR testing and placed in Universal Transport Medium (UTM). Aliquots of UTM were: 1) extracted on KingFisher Flex (Thermo Fisher Scientific, USA), MGISP-960 (MGI, China), or ExiPrep 96 Lite (Bioneer, South Korea) followed by testing with real-time reverse-transcription PCR (RT-qPCR) using TaqPath COVID-19 Combo Kits (Thermo Fisher Scientific, USA) on an ABI 7500 FAST (Thermo Fisher Scientific, USA); 2) tested directly on the Cepheid GeneXpert system using the Xpert Xpress SARS-CoV-2 (Cepheid, USA); or 3) loaded directly into a Roche cobas 6800 system and assayed with the cobas SARS-CoV-2 Test (Roche, Switzerland). The first assay targets the viral S, N, and ORF1ab gene regions. The second targets the viral N and E-gene regions, and the third targets the ORF1ab and E-gene regions.

All PCR testing was conducted at the Hamad Medical Corporation Central Laboratory or Sidra Medicine Laboratory, following standardized protocols.

Section S2. COVID-19 severity, criticality, and fatality classification

Severe Coronavirus Disease 2019 (COVID-19) disease was defined per the World health Organization (WHO) classification as a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected person with "oxygen saturation of <90% on room air, and/or respiratory rate of >30 breaths/minute in adults and children >5 years old (or ≥60 breaths/minute in children <2 months old or ≥50 breaths/minute in children 2-11 months old or ≥40 breaths/minute in children 1–5 years old), and/or signs of severe respiratory distress (accessory muscle use and inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs)".[1] Detailed WHO criteria for classifying SARS-CoV-2 infection severity can be found in the WHO technical report.[1]

Critical COVID-19 disease was defined per WHO classification as a SARS-CoV-2 infected person with "acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy".[1] Detailed WHO criteria for classifying SARS-CoV-2 infection criticality can be found in the WHO technical report.[1]

COVID-19 death was defined per WHO classification as "a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19". Detailed WHO criteria for classifying COVID-19 death can be found in the WHO technical report.[2]

Table S1. STROBE checklist for cohort studies.

	Item No	Recommendation	Main Text page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods ('Study design', paragraphs 1-4)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods ('Data sources and study design') & Figure 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods ('Data sources and study design'), Figure 1, & Section S1 in Supplementary Appendix
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods ('Study design', and 'Study outcomes'), Table 1, & Sections S1-S2 in Supplementary Appendix
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods ('Data sources', 'Study design', and 'Study outcomes'), Table 1, & Sections S1-S2 in Supplementary Appendix
Bias	9	Describe any efforts to address potential sources of bias	Methods ('Study design', paragraphs 3-4)
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods ('Study design', paragraph 3, and 'Study Outcomes') & Table 1
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods ('Statistical analysis')
		(*b*) Describe any methods used to examine subgroups and interactions	Methods ('Statistical analysis', paragraph 3)
		(*c*) Explain how missing data were addressed	NA, see Methods ('Data sources', paragraph 1)
		(*d*) If applicable, explain how loss to follow-up was addressed	NA, see Methods ('Data sources', paragraph 1)
		(*e*) Describe any sensitivity analyses	Methods ('Statistical analysis', paragraph 4)
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results ('Study population, BNT162b2 vaccine' & 'Study population for mRNA-1273 vaccine), Figure 1, & Table 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results ('Study population, BNT162b2 vaccine' & 'Study population, mRNA-1273 vaccine), Table 1, & Figure S1 & Tables S2-S3 in Supplementary Appendix
		(b) Indicate number of participants with missing data for each variable of interest	NA, see Methods ('Data sources', paragraph 1)
		(c) Summarise follow-up time (eg, average and total amount)	Results ('Effectiveness of BNT162b2 booster against Omicron' & 'Effectiveness of mRNA-1273 booster against Omicron'), Figure 2, & Table 2
Outcome data	15	Report numbers of outcome events or summary measures over time	Results ('Effectiveness of BNT162b2 booster against Omicron' & 'Effectiveness of

			mRNA-1273 booster against Omicron'), Figures 1-2, & Table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results ('Effectiveness of BNT162b2 booster against Omicron' & 'Effectiveness of mRNA-1273 booster against Omicron'), Figure 2, & Table 2
		(b) Report category boundaries when continuous variables were categorized	Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results ('Effectiveness of BNT162b2 booster against Delta' & 'Additional analyses), Figure 3, Table 3, & Figure S2 & Table S4 in Supplementary Appendix
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, paragraphs 1-4
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, paragraphs 5-6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, paragraph 7
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, paragraphs 5-6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Sources of support & Acknowledgements

Figure S1. Distribution of receipt of the booster dose by calendar month for the A) BNT162b2 and B) mRNA-1273 vaccines and distribution of the duration of follow-up in the matched cohorts of the C) BNT162b2 and D) mRNA-1273 vaccines.

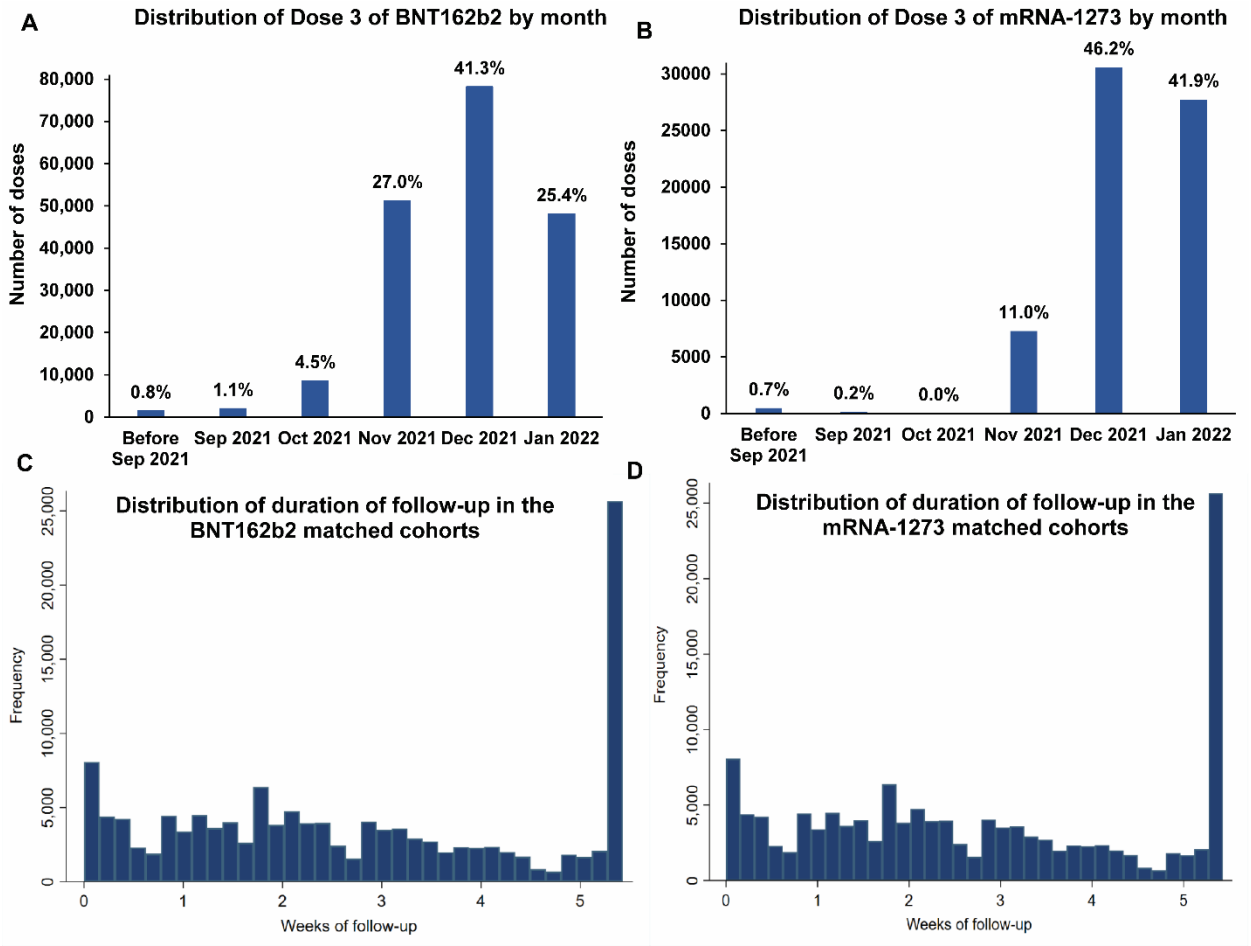


Table S2. Representativeness of study participants.

Category	
Disease, problem, or condition under investigation	Effectiveness of booster vaccination with BNT162b2 and mRNA-1273 COVID-19 vaccines, relative to the primary series of only two doses, against PCR-confirmed symptomatic infection with the SARS-CoV-2 Omicron variant and against COVID-19 hospitalization and death due to Omicron variant infection.
Special considerations related to	
Sex and gender	The effectiveness estimates were derived by comparing incidence of PCR-confirmed symptomatic infection in the booster-dose cohort and the primary-series cohort during the Omicron infection wave. Cohorts were exact-matched by sex to control for potential differences in the risk of exposure to SARS-CoV-2 infection by sex.
Age	Cohorts were exact-matched by 10-year age group to control for potential differences in the risk of exposure to SARS-CoV-2 infection by age. Nonetheless, with the young population of Qatar, our findings may not be generalizable to other countries where elderly citizens constitute a larger proportion of the total population.
Race or ethnicity group	Cohorts were exact-matched by nationality to control for potential differences in the risk of exposure to SARS-CoV-2 infection by nationality. Nationality is associated with race and ethnicity in the population of Qatar.
Geography	Individual-level data on geography were not available, but Qatar is essentially a city state and infection incidence was broadly distributed across the country's neighborhoods/areas. Cohorts were exact-matched by nationality to control for potential differences in the risk of exposure to SARS-CoV-2 infection by nationality. Qatar has unusually diverse demographics in that 89% of the population are international expatriate residents coming from over 150 countries from all world regions.
Other considerations	Individual-level data on co-morbid conditions were not available, but only a small proportion of the study population may have had serious co-morbid conditions. Only 9% of the population of Qatar are ≥50 years of age (older age as proxy for co-morbidities). The national list of persons prioritized to receive the vaccine during the first phase of vaccine roll-out included only 19,800 individuals of all age groups with serious co-morbid conditions. Individual-level data on occupation were not available but matching by nationality may have (partially) controlled the differences in occupational risk, in consideration of the association between nationality and occupation in Qatar.
Overall representativeness of this study	The study was based on the total population of Qatar and thus the study population is broadly representative of the diverse, by national background, but young and predominantly male, total population of Qatar. While there could be differences in the risk of exposure to SARS-CoV-2 infection by sex, age, and nationality, cohorts were exact-matched by these factors to control for their potential impact on our estimates for vaccine effectiveness. Given that only 9% of the population of Qatar are ≥50 years of age and the limited proportion of the population with significant co-morbidities, our estimates of effectiveness may not be generalizable to other countries where elderly citizens constitute a larger proportion of the total population or where co-morbid conditions are prevalent. With the large Omicron wave, use of rapid antigen testing was expanded to supplement PCR testing starting from January 5, 2022, but reason for testing and symptoms were not available for analysis. However, use of rapid antigen testing may not have differentially affected the investigated cohorts as it was broadly implemented.

Table S3. Distribution of the reason for testing during follow-up for A) all tests during follow-up and B) identified infections, among the matched booster-dose and primary-series cohorts for the BNT162b2 and mRNA-1273 vaccines.

	BNT162b2						mRNA-1273					
	A) All tests			B) Documented infections			A) All tests			B) Documented infections		
	Individuals who received Dose 3*	Individuals who did not receive Dose 3*	SMD†	Individuals who received Dose 3	Individuals who did not receive Dose 3	SMD†	Individuals who received Dose 3*	Individuals who did not receive Dose 3*	SMD†	Individuals who received Dose 3	Individuals who did not receive Dose 3	SMD†
Number of tests	**N=79,821**	**N=69,933**		**N=17,745**	**N=25,266**		**N=16,941**	**N=12,704**		**N=3,720**	**N=4,590**	
PCR testing-reason for testing‡												
Clinical suspicion	6,260 (7.8)	8,361 (12.0)		3,060 (17.2)	5,581 (22.1)		922 (5.4)	1,128 (8.9)		444 (11.9)	776 (16.9)	
Contact tracing	5,092 (6.4)	4,414 (6.3)		1,684 (9.5)	2,064 (8.2)		674 (4.0)	686 (5.4)		285 (7.7)	366 (8.0)	
Survey	6,243 (7.8)	6,601 (9.4)		1,311 (7.4)	2,237 (8.9)		940 (5.6)	899 (7.08)		243 (6.5)	311 (6.8)	
Individual request	2,307 (2.9)	2,255 (3.2)		687 (3.9)	1,147 (4.5)		533 (3.2)	410 (3.2)		151 (4.1)	206 (4.5)	
Pre-travel§	27,765 (34.8)	18,125 (25.9)	0.24	4,212 (23.7)	5,001 (19.8)	0.18	7,606 (44.9)	3,532 (27.8)	0.37	1,408 (37.9)	1,132 (24.7)	0.31
Port of entry	10,549 (13.2)	8,835 (12.6)		617 (3.5)	988 (3.9)		2,029 (12.0)	1,832 (14.4)		118 (3.2)	213 (4.6)	
Healthcare routine testing	978 (1.2)	1,508 (2.2)		247 (1.4)	570 (2.3)		112 (0.7)	150 (1.2)		32 (0.9)	75 (1.6)	
Other	210 (0.3)	137 (0.2)		51 (0.3)	58 (0.2)		15 (0.09)	16 (0.1)		3 (0.08)	6 (0.1)	
Rapid-antigen-testing	20,417 (25.6)	19,697 (28.2)		5,876 (33.1)	7,620 (30.2)		4,110 (24.3)	4,051 (31.9)		1,036 (27.9)	1,505 (32.8)	

Abbreviations: SMD, standardized mean difference.

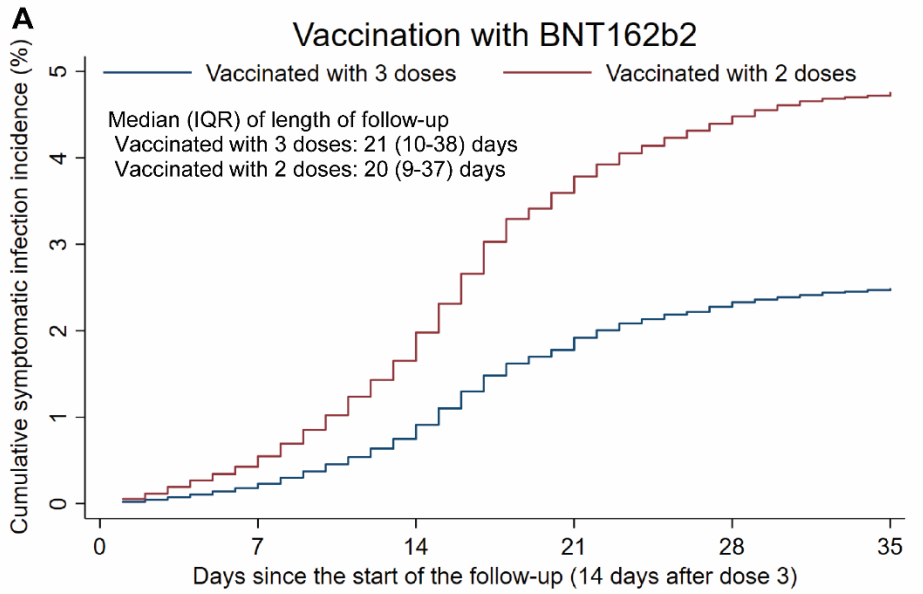
*Cohorts were matched one-to-one by sex, 10-year age group, nationality, and calendar week of second vaccine dose.

†SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation.

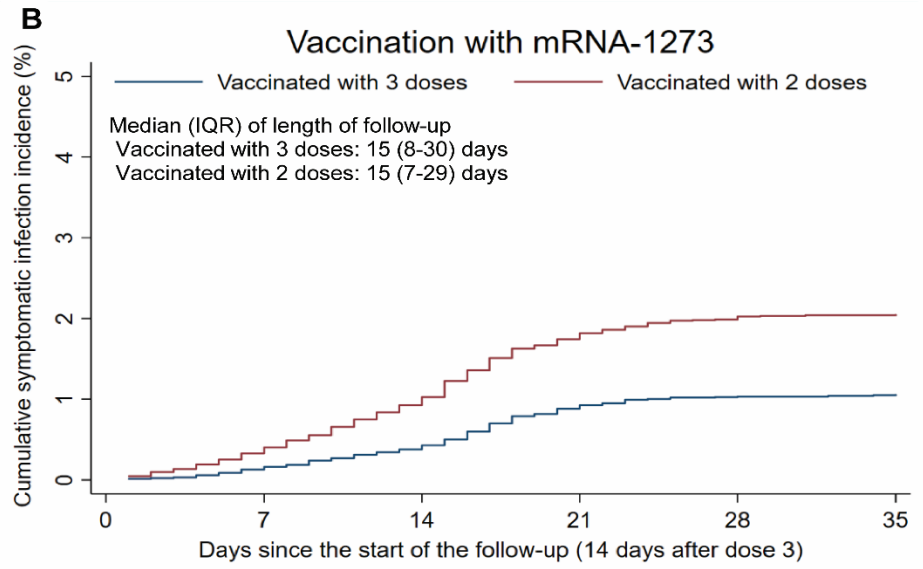
‡Every PCR test conducted in Qatar, regardless of location or setting, is classified on the basis of symptoms and the reason for testing (clinical symptoms, contact tracing, surveys or random testing campaigns, individual requests, routine healthcare testing, pre-travel, at port of entry, or other). The volume of PCR testing and the algorithm for determining who is tested have been largely stable since early 2021. Most changes to testing algorithm were related to changes in the travel-related requirements. There is only one reason assigned for each test, based on the reason indicated at the time of the testing request. Individuals have the freedom to request testing with no specific reported reason for testing, but at a personal cost ("individual request" testing). Testing for clinical suspicion due to presence of symptoms compatible with a respiratory tract infection is provided at no cost and is recorded accordingly. The same testing protocol is applied nationally and is tracked through the integrated nationwide digital-health information platform regardless of the facility at which the testing occurs.

§There were differences in the rates of routine testing between the booster-dose cohorts and the primary-series cohorts. Those in the booster-dose cohorts had higher testing rates due to higher pre-travel testing. It appears that many individuals took the booster dose in preparation for planned travel during the year-end holidays season.

Figure S2. Cumulative incidence of symptomatic Omicron infection in the matched booster-dose and primary-series cohorts for each of the BNT162b2 (A) and mRNA-1273 (B) vaccines, with start of follow-up on the 15th day after booster dose.



Time (days)	0	7	14	21	28	35
No. at risk						
Vaccinated with 3 doses	172,807	146,809	115,042	89,897	71,102	55,380
Vaccinated with 2 doses	172,807	145,505	111,465	84,065	64,667	49,503



Time (days)	0	7	14	21	28	35
No. at risk						
Vaccinated with 3 doses	55,297	43,432	31,270	22,185	15,909	10,616
Vaccinated with 2 doses	55,297	43,211	30,648	21,284	15,024	9,958

Table S4. Effectiveness of BNT162b2 and mRNA-1273 booster vaccination against Omicron, with start of follow-up on the 15th day after booster dose.

	BNT162b2		mRNA-1273	
Epidemiological measure	**Estimate (95% CI)**	**Effectiveness in % (95% CI)**	**Estimate (95% CI)**	**Effectiveness in % (95% CI)**
Total follow-up time—booster-dose cohort (person-weeks)	546,152	--	144,296	--
Total follow-up time—primary-series cohort (person-weeks)	523,116	--	141,082	--
Incidence rate for symptomatic infection—booster-dose cohort (per 10,000 person-weeks)	50.1 (48.3-52.0)	--	23.5 (21.1-26.1)	--
Incidence rate for symptomatic infection—primary-series cohort (per 10,000 person-weeks)	98.4 (95.7-101.1)	--	46.8 (43.4-50.5)	--
Adjusted hazard ratio for symptomatic infection*	0.50 (0.48-0.52)	49.9 (47.6-52.2)	0.48 (0.42-0.55)	52.0 (45.1-57.9)

Abbreviations: CI, confidence interval.

*Cox regression analysis adjusted for sex, 10 age-groups, 10 nationality groups, and calendar week of second vaccine dose.

References

1. World Health Organization. COVID-19 clinical management: living guidance. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. Accessed on: May 15 2021. 2021.
2. World Health Organization. International guidelines for certification and classification (coding) of COVID-19 as cause of death. Available from: https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19-20200420-EN.pdf?ua=1. Document Number: WHO/HQ/DDI/DNA/CAT. Accessed on May 31, 2021. 2021.