

## **SARS-CoV-2 vaccination to support safe surgery during the pandemic: a modelling study using data from an international prospective cohort study**

### **Appendix S1 Supplementary material**

#### *Case fatality rate in the general population*

The UK Office for National Statistics (ONS) runs the Coronavirus (COVID-19) Infection Survey, a repeated cross-sectional survey<sup>1</sup>. The survey is based on people from randomly selected private households submitting nose and throat swabs for SARS-CoV-2 analysis (real-time reverse transcriptase polymerase chain reaction, RT-PCR assay). The survey is based on a large sample size, with several hundred thousand individuals submitting swabs for laboratory analysis, including both people with and without symptoms.

Based on the Coronavirus (COVID-19) Infection Survey results, the ONS publishes modelled estimates for new cases per day per 10,000 population<sup>1</sup>. To obtain estimates for total infections, each daily estimate for England was multiplied by the ONS estimate for England's adult ( $\geq 18$  years) population in 2019 ( $n=43,004,640$ )<sup>2</sup>. Daily estimated cases were summed to calculate total cases within the period of interest.

To calculate a case fatality rate, estimates for SARS-CoV-2 incidence were matched to data COVID-19 death statistics. Among patients who die with COVID-19, there is typically a time lag between SARS-CoV-2 diagnosis and death of around 4 weeks<sup>3-5</sup>. Therefore, we matched estimates for SARS-CoV-2 cases to COVID-19 deaths four weeks later. In order to reduce imprecisions in this methodology due to fluctuating SARS-CoV-2 incidence, case data were taken from a period when SARS-CoV-2 incidence was relatively stable in England: 28 May 2020 to 26 August 2020. During this period there was a median of 0.27 per 10,000 population (interquartile range 0.26-0.30) daily new SARS-CoV-2 cases in England.

Based on the ONS incidence point estimates, we calculated that during the 13 weeks from 28 May 2020 to 26 August 2020 there were a total of 115,252 SARS-CoV-2 cases in adults in England. This compares to 64,552 total cases detected during this period in people aged  $\geq 20$  years through diagnostic testing in hospitals and the community<sup>6</sup>.

The ONS did not provide age-stratified incidence estimates throughout the full time period 28 May 2020 to 26 August 2020. However, NHS Test & Trace provided a breakdown of the 64,552 cases detected in this period: 38,336 (59.4%) were in people aged 20-49 years, 14,917 (23.1%) were people aged 50-69 years, and 11,299 (17.5%) were in people aged  $\geq 70$  years<sup>6</sup>. Applying these ratios to the projected total of 115,252 SARS-CoV-2 cases in England, produced estimates of 68,446 cases in people aged 20-49 years, 26,633 in people aged 50-69 years, and 20,173 cases in people aged  $\geq 70$  years. Data were collated for the age group 20-49 years rather than 18-49 years as these are the data cut-offs publicly available.

UK Coronavirus Dashboard<sup>7</sup> data on deaths within 28 days of SARS-CoV-2 diagnosis were accessed for the period 25 June 2020 to 23 September 2020 (window shifted four weeks forward from that for estimating cases). During this period in England there were 38 deaths within 28 days of SARS-CoV-2 diagnosis in people aged 20-49 years, 227 deaths in people aged 60-69 years, and 1,194 deaths in people aged  $\geq 70$  years.

Based on the above figures, the case fatality rate for SARS-CoV-2 in the general population in England was estimated to be 0.06% in people aged 20-49 years, 0.84% in people aged 50-69 years, and 5.92% in people aged  $\geq 70$  years.

#### *Case fatality rate in the general population: sensitivity analyses*

Based on the lower and upper bounds of the credible intervals published by ONS, the total cases during the 13 weeks from 28 May 2020 to 26 August 2020 could have been between 78,871 and 161,740.

Based on the lower bound estimate for SARS-CoV-2 cases (78,871) it was projected there would have been of 46,840 cases in people aged 20-49 years, 18,226 in people aged 50-69 years, and 13,805 cases in people aged  $\geq 70$  years. Therefore, for the best-case scenario (lowest NNV), case fatality rates were calculated as 0.08% in people aged 20-49 years, 1.23% in people aged 50-69 years, and 8.65% in people aged  $\geq 70$  years.

Based on the lower bound estimate for SARS-CoV-2 cases (161,740) it was projected there would have been of 96,054 cases in people aged 20-49 years, 37,376 in people aged 50-69 years, and 28,310 cases in people aged  $\geq 70$  years. Therefore, for the worst-case scenario (highest

NNV), case fatality rates were calculated as 0.04% in people aged 20-49 years, 0.60% in people aged 50-69 years, and 4.22% in people aged  $\geq 70$  years.

*Calculation of NNV to prevent one COVID-19-related death over 30 days following vaccination*

To calculate NNV to prevent one death over 30 days following vaccination in the surgical groups:

$$\text{NNV} = 1 / S$$

S: Postoperative mortality (within 30 days following surgery) attributable to SARS-CoV-2 infection

To calculate NNV to prevent one death over 30 days following vaccination in the general population:

$$\text{NNV} = 1 / (D * 30 * C)$$

D: Daily community SARS-CoV-2 incidence

C: Case fatality rate for SARS-CoV-2 in the general population

*COVID-19-related deaths prevented*

The number of COVID-19-related deaths that would be prevented in one year preoperatively vaccinating surgical patients rather than age-matched controls was calculated separately for subgroups stratified by age (18-49 years, 50-69 years,  $\geq 70$  years) and indication (cancer, non-cancer).

$$\text{Additional lives saved} = (V * P * M * I * R) - (V * P * M * D * 30 * CFR)$$

V: Total pre-pandemic annual surgical volume

P: Proportion of all surgery that is performed in subgroup of interest

M: Estimated global surgical volume in 2021 as a proportion of pre-pandemic volume

- I: Postoperative SARS-CoV-2 rate in the first 30 days following surgery
- R: Average marginal effect for mortality between patients who did and did not have postoperative SARS-CoV-2 infection
- D: Daily community SARS-CoV-2 incidence
- C: Case fatality rate for SARS-CoV-2 in the general population

$V * P * M$  produces the absolute global total for subgroup surgical volume over one year.

$V * P * M * I * R$  produces the subgroup annual total for lives saved in the first 30 postoperative days by preoperatively vaccinating surgical patients.

$V * P * M * D * 30 * C$  produces an annual total for lives saved over 30 days by vaccinating the same number of age-matched individuals from the general population.

The pre-pandemic total annual global volume of elective surgery has been estimated as 170,195,382 procedures, including both inpatient and elective procedures. Data from GlobalSurg-CovidSurg Week was used to estimate the proportion of all surgery that is performed in each subgroup of interest (Supplementary Table 5); the denominator for these calculations included both day case patients and patients with preoperative SARS-CoV-2 infection (Supplementary Figure 1).

#### *Sensitivity analyses for community SARS-CoV-2 incidence*

Daily community SARS-CoV-2 incidence data was available from Our World in Data for 183 of 193 United Nations member states<sup>8</sup>. The 10 countries without SARS-CoV-2 data (Kiribati, Micronesia, Nauru, North Korea, Palau, St. Kitts and Nevis, Timor-Leste, Tonga, Turkmenistan, Tuvalu) were excluded from this analysis.

For each country, average daily community SARS-CoV-2 incidence data was considered from the date when it confirmed 100 cumulative SARS-CoV-2 cases, through to 31 December 2020. Seven countries (Dominica, Fiji, Laos, Marshall Islands, Samoa, Solomon Islands, Vanuatu) recorded fewer than 100 SARS-CoV-2 cases in 2020. These countries were assigned SARS-

CoV-2 incidence values equivalent to the country with the lowest average rate (Tanzania: 0.027 cases per million population per day).

Countries were ranked by the calculated average daily SARS-CoV-2 incidence and split into tertiles (Supplementary Table 6). Median daily community SARS-CoV-2 incidence was calculated for each tertile to produce values for low, medium, and high community SARS-CoV-2 incidence. The main analysis was based on medium SARS-CoV-2 incidence (26.48 cases per million population per day). The low (1.54 cases per million population per day) and high (120.56 cases per million population per day) community SARS-CoV-2 incidence rates were used in the sensitivity analyses.

#### *Best- and worst-case scenarios*

To further explore uncertainty, in addition to the main analysis, best- and worst-case scenarios were produced. The best-case scenario represents the lowest likely value for NNV and the highest likely value for additional COVID-19-related deaths prevented, whereas the worst-case scenario represents the highest likely value for NNV and the lowest likely value for additional COVID-19-related deaths prevented.

The best- and worst-case scenarios are based around the key areas of uncertainty:

- Case fatality rate in the general population: NNV will be more favourable (lower NNV) the higher the case fatality rate is. The ONS provides credible intervals for their estimates of SARS-CoV-2 incidence. For the best-case scenario, the lower bounds for the credible intervals were used (thereby reducing the denominator for case fatality rate calculation, producing the highest likely baseline case fatality rate). For the worst-case scenario, the upper bounds for the credible intervals were used.
- Postoperative SARS-CoV-2 rates: 95% confidence intervals were calculated for these rates. For the best-case scenario, upper bounds were used, and for the worst-case scenario, the lower bounds were used.

- Postoperative mortality attributable to SARS-CoV-2: 95% confidence intervals were calculated for the average marginal effects. For the best-case scenario, upper bounds were used, and for the worst-case scenario, the lower bounds were used.
- Vaccine effectiveness: no deaths due to COVID-19 have been reported beyond 1 week following SARS-CoV-2 vaccination in the phase III trials published to date, although these trials were not designed to detect mortality differences<sup>9-12</sup>. In the main analysis vaccines were modelled as having 95% effectiveness. For the best-case scenario effectiveness was modelled as 100%, and for the worst-case scenario effectiveness was modelled as 80%.

The parameters used in the sensitivity analyses are summarised in Table 1.

*Comparison of general population case fatality rate estimates to published literature*

There are few high-quality, age-stratified studies of overall SARS-CoV-2 case fatality rates for the general population, capturing both community and hospital deaths. Regional variation in availability of SARS-CoV-2 testing makes it difficult to calculate reliable case fatality rates using reported SARS-CoV-2 incidence statistics, as these are likely to substantially underestimate the true numbers of cases and therefore overestimate case fatality rates. More accurate incidence data can be obtained from population surveillance studies.

The case fatality rates calculated in this analysis are consistent with previously published estimates from a study based on seroprevalence data from 45 countries. This found case fatality rates to be <0.5% in people aged 20-64 years, around 1% in people aged 65-69 years, around 2-8% in people aged  $\geq 70$  years<sup>13</sup>. However, from the publicly available data, it was not possible to obtain overall estimates for case fatality rates in people aged 18-49 years versus 50-69 years versus  $\geq 70$  years.

*Comparison of general population NNV estimates to published literature*

Peer-reviewed estimates are not available for NNV for SARS-CoV-2 in the general population. In this analysis there was a pattern of increasing NNV with decreasing age. This is consistent with a previous analysis by the COVID Actuaries Response Group. They produced estimates for

NNV based on the number of deaths due to COVID-19 recorded in England from the start of the pandemic to 20 November 2020<sup>14</sup>. They found that the NNV was 20 for vaccination of care home residents, 160 for people aged over 80 years, 350 for people aged over 75 years, 600 for people aged over 70 years, increasing to 47,000 for people aged under 50 years. In the period February to November 2020 the United Kingdom was amongst the top 10 countries in the world for SARS-CoV-2 cases per capita. As NNV varies depending on disease incidence, NNV estimates from England will be lower than global NNV estimates; this explains why NNV values in our analysis were higher.

## References

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**Table S1 Overall global 30-day postoperative SARS-CoV-2 rates following inpatient elective surgery**

	Point estimate	95% confidence interval
Age 18-49 years		
Elective non-cancer surgery	0.68% (124/18241)	0.57%-0.81%
Elective cancer surgery	1.00% (36/3595)	0.70%-1.38%
Age 50-69 years		
Elective non-cancer surgery	0.79% (110/13906)	0.65%-0.95%
Elective cancer surgery	1.56% (120/7671)	1.30%-1.87%
Age $\geq$ 70 years		
Elective non-cancer surgery	0.87% (69/7932)	0.68%-1.10%
Elective cancer surgery	1.56% (8/5244)	1.25%-1.94%

**Table S2 Unadjusted and adjusted model for 30-day mortality in elective inpatient surgery patients aged 18-49 years**

Factor	Unadjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
<b>Age</b>				
18-29 years	Reference	-	Reference	-
30-39 years	0.79 (0.42-1.46)	0.450	0.69 (0.37-1.29)	0.239
40-49 years	1.62 (0.94-2.76)	0.080	0.99 (0.56-1.73)	0.968
<b>Sex</b>				
Female	Reference	-	Reference	-
Male	1.55 (1.00-2.38)	0.047	1.45 (0.93-2.26)	0.102
<b>ASA</b>				
Grades 1-2	Reference	-	Reference	-
Grades 3-5	8.36 (5.30-13.17)	<0.001	6.69 (4.19-10.69)	<0.001
<b>Indication</b>				
Non-cancer surgery	Reference	-	Reference	-
Cancer surgery	4.67 (2.98-7.33)	<0.001	3.92 (2.45-6.27)	<0.001
<b>Grade of surgery</b>				
Minor	Reference	-	Reference	-
Major	1.55 (0.89-2.68)	0.121	1.19 (0.67-2.10)	0.546
<b>Postoperative SARS-CoV-2</b>				
No	Reference	-	Reference	-
Yes	5.31 (1.60-17.60)	0.006	4.07 (1.18-14.13)	0.027

ASA: American Society of Anesthesiologists physical status grade; CI: confidence interval; OR: odds ratio

Multilevel models including country and hospital effects were used for both unadjusted and adjusted analyses. The adjusted analysis was adjusted for age, sex, ASA grade, surgical indication, grade of surgery, and postoperative SARS-CoV-2 infection.

**Table S3 Unadjusted and adjusted model for 30-day mortality in elective inpatient surgery patients aged 50-69 years**

Factor	Unadjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
50-59 years	Reference	-	Reference	-
60-69 years	1.44 (1.08-1.91)	0.013	1.22 (0.91-1.64)	0.190
Sex				
Female	Reference	-	Reference	-
Male	1.32 (1.00-1.75)	<0.001	1.17 (0.87-1.57)	0.299
ASA				
Grades 1-2	Reference	-	Reference	-
Grades 3-5	5.71 (4.16-7.83)	0.053	5.24 (3.79-7.24)	<0.001
Indication				
Non-cancer surgery	Reference	-	Reference	-
Cancer surgery	2.32 (1.72-3.12)	<0.001	2.07 (1.53-2.82)	<0.001
Grade of surgery				
Minor	Reference	-	Reference	-
Major	1.38 (0.96-1.98)	0.082	1.04 (0.72-1.52)	0.824
Postoperative SARS-CoV-2				
No	Reference	-	Reference	-
Yes	13.67 (7.76-24.08)	<0.001	11.52 (6.30-21.09)	<0.001

ASA: American Society of Anesthesiologists physical status grade; CI: confidence interval; OR: odds ratio

Multilevel models including country and hospital effects were used for both unadjusted and adjusted analyses. The adjusted analysis was adjusted for age, sex, ASA grade, surgical indication, grade of surgery, and postoperative SARS-CoV-2 infection.

**Table S4 Unadjusted and adjusted model for 30-day mortality in elective inpatient surgery patients aged  $\geq 70$  years**

Factor	Unadjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
<b>Age</b>				
70-79 years	Reference	-	Reference	-
$\geq 80$ years	1.86 (1.41-2.44)	<0.001	1.66 (1.25-2.20)	<0.001
<b>Sex</b>				
Female	Reference	-	Reference	-
Male	1.56 (1.18-2.06)	0.002	1.51 (1.14-2.01)	0.004
<b>ASA</b>				
Grades 1-2	Reference	-	Reference	-
Grades 3-5	5.17 (3.61-7.41)	<0.001	4.44 (3.09-6.38)	<0.001
<b>Indication</b>				
Non-cancer surgery	Reference	-	Reference	-
Cancer surgery	1.97 (1.49-2.61)	<0.001	1.85 (1.39-2.46)	<0.001
<b>Grade of surgery</b>				
Minor	Reference	-	Reference	-
Major	1.63 (1.14-2.34)	0.008	1.52 (1.05-2.19)	0.027
<b>Postoperative SARS-CoV-2</b>				
No	Reference	-	Reference	-
Yes	13.41 (8.20-21.94)	<0.001	10.31 (6.18-17.20)	<0.001

ASA: American Society of Anesthesiologists physical status grade; CI: confidence interval; OR: odds ratio

Multilevel models including country and hospital effects were used for both unadjusted and adjusted analyses. The adjusted analysis was adjusted for age, sex, ASA grade, surgical indication, grade of surgery, and postoperative SARS-CoV-2 infection.

**Table S5 Estimates for surgical case-mix and pre-pandemic annual volume for elective inpatient surgery**

	Case-mix (95% CI)*	Pre-pandemic annual volume
<b>Age 18-49 years</b>		
Elective non-cancer surgery	20.44% (20.18%-20.71%)	34,794,436
Elective cancer surgery	4.03% (3.90%-4.16%)	6,857,410
<b>Age 50-69 years</b>		
Elective non-cancer surgery	15.59% (15.35%-15.82%)	26,525,494
Elective cancer surgery	8.60% (8.41%-8.78%)	14,632,327
<b>Age <math>\geq</math>70 years</b>		
Elective non-cancer surgery	8.89% (8.70%-9.08%)	15,130,181
Elective cancer surgery	5.88% (5.72%-6.03%)	10,002,859

CI: confidence interval

Case-mix indicates the proportion of all elective surgery that is accounted for by each subgroup. The denominator (170,195,382 surgeries per year) is the pre-pandemic annual global total for all elective surgeries. This includes both daycare and inpatient surgery, and all patients regardless of SARS-CoV-2 status. Annual pre-pandemic volume was calculated for each group using the point estimate for case-mix.

Please note that due to the case-mix estimates presented being rounded, replication of the calculation may lead to different surgical volume values to those reported in the table.

**Table S6 Country-level average daily SARS-CoV-2 incidence rates for 2020**

Tertile 1		Tertile 2		Tertile 3	
Tanzania	0.03	Japan	5.92	Albania	71.24
Dominica*	0.03	Ghana	6.26	Estonia	71.81
Fiji*	0.03	Antigua and Barbuda	6.49	United Arab Emirates	72.67
Laos*	0.03	Kenya	6.54	Russia	73.89
Marshall Islands*	0.03	Sri Lanka	7.13	Belarus	74.19
Samoa*	0.03	Pakistan	7.47	Latvia	75.4
Solomon Islands*	0.03	Algeria	7.94	Azerbaijan	76.73
Vanuatu*	0.03	Lesotho	7.96	Cabo Verde	84.53
Vietnam	0.05	Uzbekistan	8.24	Ukraine	88.13
Cambodia	0.06	Myanmar	8.91	Cyprus	88.13
China	0.19	Gambia	9.29	Bahamas	88.65
Yemen	0.29	Indonesia	9.3	Oman	89.74
Burundi	0.31	Seychelles	9.41	Lebanon	91.02
Thailand	0.35	Bangladesh	11.55	Denmark	95.35
Niger	0.49	Malaysia	11.71	Maldives	99.97
Papua New Guinea	0.51	St. Vincent and the Grenadines	12.96	Malta	101.15
Chad	0.51	Mauritania	13.53	Jordan	101.24
Brunei Darussalam	0.53	Venezuela	14.2	Bulgaria	101.38
Democratic Republic of the Congo	0.71	Equatorial Guinea	14.69	Monaco	101.93
Benin	1.09	Philippines	14.76	Peru	106.16
Burkina Faso	1.12	Gabon	16.46	Chile	109.08
Somalia	1.13	Jamaica	16.5	Italy	111.34
Mauritius	1.22	Trinidad and Tobago	18.53	Colombia	111.71
Sierra Leone	1.27	Sao Tome and Principe	18.76	Romania	112.15
Liberia	1.3	Uruguay	19.08	Slovakia	113.74
South Sudan	1.31	Djibouti	21.68	Costa Rica	116.16
Mali	1.31	Finland	22.13	Hungary	116.7
Mongolia	1.49	St. Lucia	24.04	Poland	116.76
Nigeria	1.53	Grenada	24.44	Bosnia and Herzegovina	118.6
New Zealand	1.54	India	25.39	Kuwait	120.28
Malawi	1.54	El Salvador	26.48	United Kingdom	120.56
Eritrea	1.73	Guatemala	28.94	Brazil	122.83
Togo	1.73	Norway	30.32	Argentina	125.31
Sudan	2.27	Eswatini	32.47	Moldova	126.33
Rwanda	2.35	Singapore	32.57	France	133.62
Madagascar	2.4	Guyana	33.6	Austria	133.96
Mozambique	2.53	Botswana	33.64	Spain	135.21
Angola	2.59	Saudi Arabia	35.55	Portugal	137.97
Syria	2.93	Nepal	37.41	North Macedonia	140.2
Cote d'Ivoire	3.03	Kazakhstan	38.12	Sweden	149.58
Uganda	3.2	Mexico	38.27	Netherlands	156.72
Cameroon	3.55	Tunisia	41.57	Israel	166.3
Haiti	3.62	Ecuador	41.67	Qatar	168.63
Cuba	3.73	Morocco	41.74	Serbia	172.39
Australia	3.74	Honduras	44.21	Switzerland	173.01
South Korea	3.81	Kyrgyz Republic	44.95	Croatia	178.26
Guinea	3.82	Greece	45.28	Lithuania	181.09
Comoros	3.92	Iran	47.05	Belize	181.65
Nicaragua	4	Namibia	49.43	Bahrain	183.19
Senegal	4.05	Bolivia	49.67	Belgium	185.31
Ethiopia	4.19	Suriname	49.92	Armenia	186.69
Central African Republic	4.24	Iraq	50.33	Panama	198.53
Zimbabwe	4.24	Canada	52.3	Slovenia	199.71
Zambia	4.56	Dominican Republic	55.02	United States	200.02
Egypt	4.6	Paraguay	55.79	Georgia	205.73
Afghanistan	4.74	Iceland	56.31	Czech Republic	228.23
Bhutan	4.77	Turkey	57.23	San Marino	236.93
Republic of the Congo	4.89	South Africa	61.67	Luxembourg	255.26
Guinea-Bissau	4.89	Ireland	63.37	Montenegro	277.8
Barbados	5.7	Libya	66.88	Andorra	361.53
Tajikistan	5.7	Germany	68.67	Liechtenstein	410.87
Tertile 1 median	1.54	Tertile 2 median	26.48	Tertile 3 median	120.56

Figures reported as averaged daily SARS-CoV-2 cases per million population per day from the date when the country confirmed 100 cumulative SARS-CoV-2 cases, through to 31 December 2020.

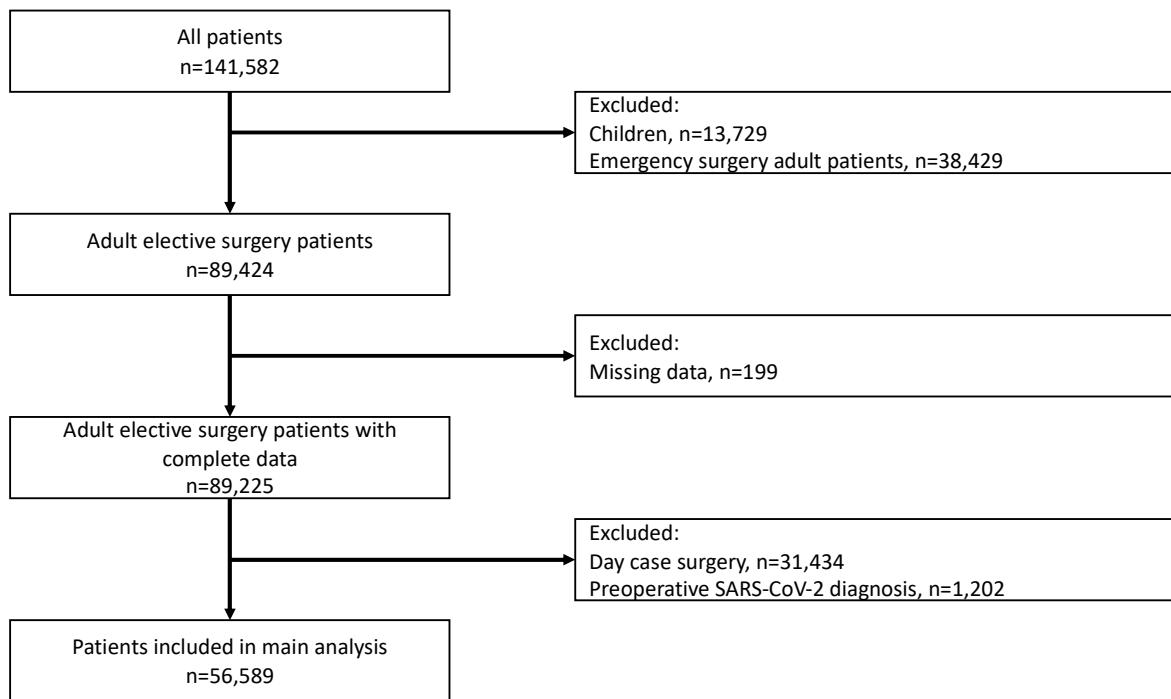
\*Seven countries recorded fewer than 100 SARS-CoV-2 cases in 2020. These countries were assigned SARS-CoV-2 incidence values equivalent to the country with the lowest average rate.

**Table S7 Additional COVID-19-related deaths prevented within 30 days of surgery if surgical patients were vaccinated preoperatively in preference to age-matched controls from the general population**

<b>2021 surgical volume as proportion of pre-pandemic annual volume</b>	<b>18-49 years</b>	<b>50-69 years</b>	<b>≥70 years</b>
25%	856 (0-2,967)	9,831 (3,437-18,566)	8,875 (3,288-16,803)
50%	1,713 (0-5,934)	19,663 (6,875-37,131)	17,749 (6,576-33,607)
75%	2,569 (0-8,900)	29,494 (10,312-55,697)	26,624 (9,865-50,410)
100%	3,425 (0-11,867)	39,325 (13,750-74,262)	35,498 (13,154-67,213)

Figures presented based on a range of different projections for 2021 surgical volume as a proportion of pre-pandemic volume. Estimates are based on the medium community SARS-CoV-2 infection rates. Ranges in parentheses indicate results from worst- and best-case scenarios.

**Fig. S1 Flowchart for inclusion of GlobalSurg-CovidSurg Week data**



ASA: American Society of Anesthesiologists physical status grade

\*This denominator was used for estimating case-mix  
Analysis included patients whose data was available as of 4 February 2021.