

1 **Vaccines provide disproportional protection to the increased hospitalisation risk posed**
2 **by the Delta variant of SARS-CoV2: a meta-analysis**

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11 **Abstract**

12 Variants of SARS-CoV2 that achieved global dominance (Alpha and Delta) have been
13 associated with increased hospitalisation risk. A quantification of this risk across studies is
14 currently lacking for Delta. Furthermore, how risk for severe disease changes in both
15 vaccinated and unvaccinated individuals is important as the underlying risks determine public
16 health impact. The surplus risk of Delta versus Alpha on hospitalisation was determined
17 using random-effects meta-analysis. Infection with the Delta compared to the Alpha variant
18 increased hospitalisation risk (unvaccinated: log HR 0.62, CI: 0.41 – 0.84, $P < 0.0001$; linear
19 HR 1.87). This finding should inform our response to future variants of concern, currently
20 Omicron. SARS-CoV2 variants that achieve dominance, have achieved this through a higher
21 rate of infection and this evolutionary trajectory has also come with a correlated higher risk
22 of severe disease. The surplus risk posed by Delta was significantly lower however in the
23 vaccinated (model estimate -0.40, CI: -0.73 – -0.07, $P = 0.017$). Vaccination thus provided a
24 disproportionate level of protection to hospitalisation with the Delta variant and provides
25 further rationale for vaccination for SARS-CoV2 as a durable public health measure.

26 **Main text**

27

28 During the SARS-CoV2 pandemic a key question was do vaccines work? After the
29 emergence of variants focus shifted to whether vaccines still provide protection. Both these
30 questions have been answered with a resounding yes thus far¹. However, a largely overlooked
31 and understudied question has been if vaccines protect against the increased severe disease
32 risk that has now been suggested for the two variants that achieved global dominance, Alpha
33 (B.1.1.7)²⁻⁴ and Delta (B.1.617)⁵. A quantification of this risk and its interplay with the
34 protection offered by vaccination across studies is currently lacking for Delta. Vaccines could
35 provide proportional protection, i.e. lower the increased hazard of hospitalisation posed by a
36 variant by a similar proportional amount, could be escaped or provide disproportional
37 protection. Note, such an analysis is different to studying vaccine effectiveness, as this is a
38 ratio of risks resulting from infection with the same variant. The consideration of how risk
39 changes with a new variant is of utmost concern. Even when vaccine effectiveness is
40 unaffected, the underlying risks for both categories, vaccinated and unvaccinated can still be
41 higher (or lower), changing the impact on public health of a variant. The recent emergence of
42 Omicron has again highlighted this importance.

43

44 Hospitalisation risk was used as a proxy for disease severity and a meta-analysis was
45 performed across studies to quantify the risk of the Alpha versus the Delta variant in the
46 unvaccinated and vaccinated. The number of studies that estimated the hospitalisation risk of
47 Delta versus Alpha for both vaccinated and unvaccinated individuals is relatively low.
48 Perhaps explained by the demand put on the data to conduct such analyses. Longitudinal data
49 on patients and their outcomes are required and only during the rapid gain in dominance of
50 Delta can reliable comparisons be made. Moreover, adjustment for differences in
51 confounding variables, such as age, are required for effective estimation of the true effect⁴.
52 Five studies⁵⁻⁹ included estimates for both vaccinated and unvaccinated individuals. Three
53 studies¹⁰⁻¹² were identified with known vaccination status from which the hospitalisation risk
54 of Delta could be extracted only for the unvaccinated. Vaccination was not separated by
55 vaccine type in these studies but given the countries where the included studies were
56 conducted in, the vaccines used are a combination of BNT162b2, mRNA-1273 and
57 ChAdOx1 nCoV-19.

58

59 Infection with the Delta compared to the Alpha variant increased hospitalisation risk (Figure
60 1; Table S1; unvaccinated: log HR 0.62, CI: 0.41 – 0.84, $P < 0.0001$; linear HR 1.87). This
61 risk was significantly lower in the vaccinated individuals (Table S1, model estimate of
62 vaccination: log HR -0.40, CI: -0.73 – -0.07, $P = 0.017$). When data was split for first and
63 second doses, second doses showed the strongest response (Table S2, but note only two
64 studies included estimates for single dosage). Estimates of these vaccination status specific
65 risks remained similar and statistically significant when the three studies that only estimated
66 risk in the unvaccinated were excluded (Table S3-S4). Within the vaccinated individuals
67 there was an increased risk posed by Delta (log HR 0.20, CI: -0.1766 – 0.5842; linear HR
68 1.22) but this was not significantly different from zero ($P = 0.29$). Vaccination provides a
69 disproportionate level of protection to hospitalisation with the Delta variant.

70

71 As with the Alpha variant, the Delta variant is associated with a larger risk of severe disease,
72 most prominent in the unvaccinated. This finding should inform our response to future
73 variants of concern, currently Omicron. SARS-CoV2 variants that achieve dominance, have
74 achieved this through a higher rate of infection and this evolutionary trajectory has also come
75 with a correlated higher risk of severe disease. These consequences were now seen twice
76 during the pandemic, with both Alpha and Delta. Fortunately, vaccination reduces
77 hospitalisation risk. For Delta there is even a disproportionate rescue of surplus
78 hospitalisation risk compared to Alpha (Figure 1), and limited data available for Alpha also
79 support this notion compared to the wildtype variant (two studies^{7,13}, Table S5). Such a
80 response could be due to several currently unknown reasons. For example, specific aspects of
81 immunity¹⁴ primed by vaccination or a disproportionate rescue by vaccination of the gained
82 virulence of variants of concern.

83

84 The data summarised here through meta-analysis provide unique insight into how variants of
85 concern have impacted the SARS-CoV2 pandemic. The disproportionate rescue from
86 hospitalisation risk through vaccination identified provides additional support for vaccination
87 as a durable public health intervention. The gain in virulence in both Alpha and Delta in the
88 unvaccinated does pose a warning for future variants when vaccination coverage is low or
89 spread of the variant is wide. In practice, estimating the impact of novel variants of concern
90 on risk to develop severe disease can only be conducted on a very small timescale and easily
91 becomes confounded⁴ by e.g. improvements in treatment, changes in demography and
92 vaccine waning¹⁵. With both Alpha, and Delta, and now Omicron, a loss (or regain) of

93 template amplification in the majority of qPCR tests provided a reliable and convenient proxy
94 for which variant a patient is infected with. Future variants need not provide such
95 convenience. Moreover, the faster a variant gains dominance the smaller the time window in
96 which accurate comparisons can be made. In that case, in a public health setting a rapid shift
97 in the demography (e.g. vaccinated versus unvaccinated) and number of hospitalisations over
98 time is probably most informative of the severity of a variant of concern identified and its
99 interaction with vaccination status. The prior known history of evolutionarily successful
100 variants showing increased severe disease risk would however warrant caution upon
101 identification of spread of a novel variant over relying on real-time data.

102

103 **Methods**

104 Literature search (final search 10 December 2021) was conducted in Google Scholar using
105 the following search terms: "hospitalisation OR hospitalization" risk B.1.1.7 B.1.617
106 vaccinated ("hazard ratio" OR HR). Inclusion criteria were that hospitalisation risk of Delta
107 versus Alpha infection was reported per vaccination category. Hospitalisation risk did not
108 include emergency room attendance if this was reported separately. Adjusted hazard (or risk)
109 ratios were extracted as adjusted for the covariates included in each study. No exclusion
110 criteria were formulated. The search yielded 230 results (see PRISMA guide, Figure S1) and
111 returned 8 eligible studies. For the post-hoc search for Alpha specific papers (yielding two
112 studies), the literature was queried again and references within papers collated for the Delta
113 search selecting for studies that included estimates for both vaccinated and unvaccinated
114 individuals. We collected adjusted hazard or risk ratios as reported in text, tables or derived
115 from combining coefficients from models reported. These were log (natural) transformed and
116 the corresponding standard errors were derived from the reported linear confidence intervals
117 for use in meta-analysis. Random effects meta-analysis was conducted in *metafor*¹⁶ in R and
118 included study as a random term, to correct for multiple effect sizes per study.

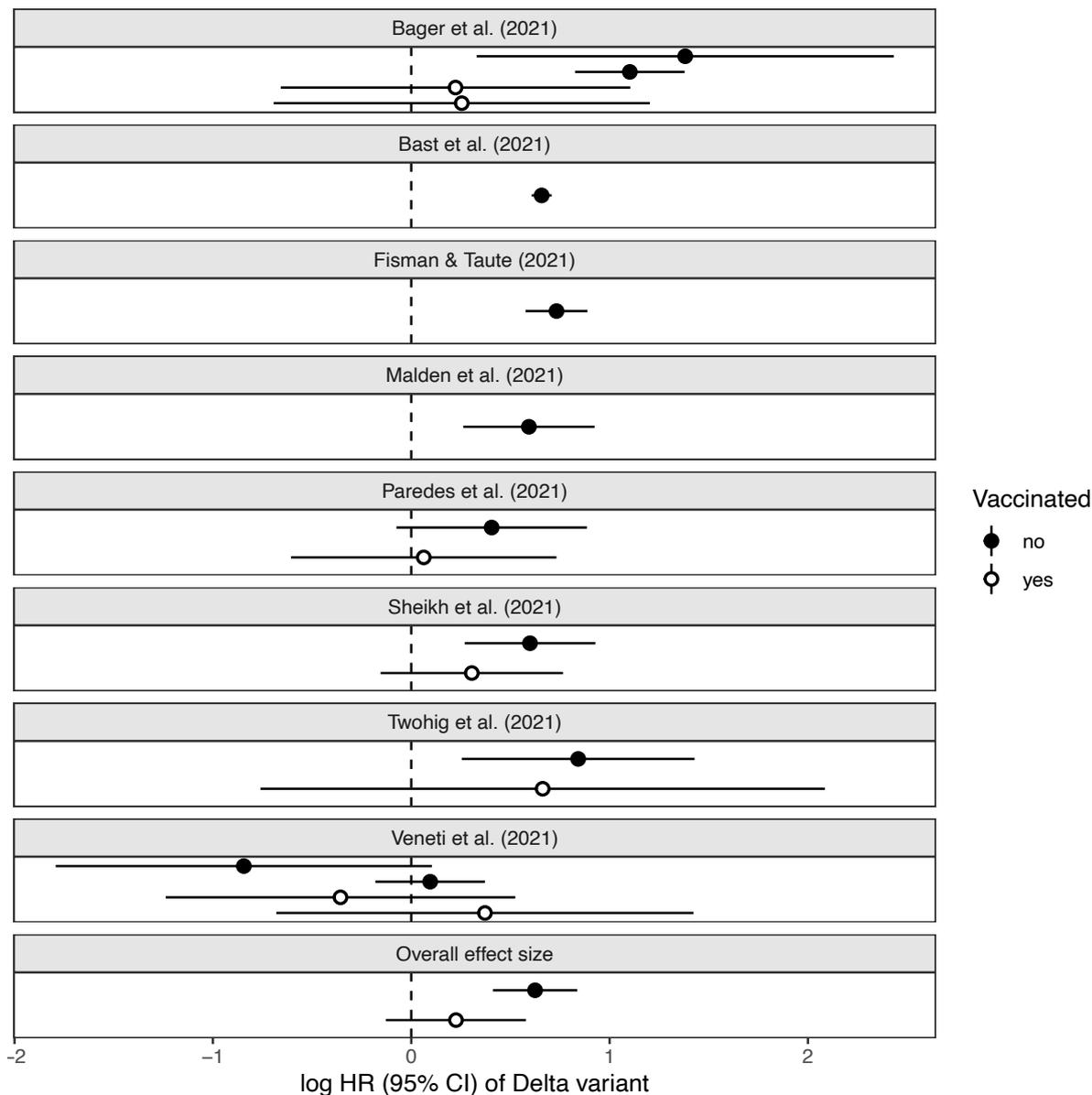
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120 **Funding**

121 Sir Henry Dale Fellowship (Wellcome and Royal Society; 216405/Z/19/Z) and an Academy
122 of Medical Sciences Springboard Award (the Wellcome Trust, the Government Department
123 of Business, Energy and Industrial Strategy (BEIS), the British Heart Foundation and
124 Diabetes UK).

125 **Figures**

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129 **Figure 1.** Individual effect sizes per study for hospitalisation risk of Delta versus Alpha, split
130 for vaccination status. Overall effect sizes as estimated through random-effects meta-analysis
131 are shown at the bottom of the figure.

132 **Supplementary Tables**

133

134 **Table S1.** Meta-analytic model estimating the risk of Delta versus Alpha for hospitalisation
135 across the 8 studies included.

	log HR estimate	CI lower	CI upper	P
unvaccinated (reference)	0.624	0.412	0.837	< 0.0001
vaccinated	-0.399	-0.726	-0.072	0.017

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138 **Table S2.** Meta-analytic model estimating the risk of Delta versus Alpha for hospitalisation
139 across the 8 studies included, separated by vaccination dose. Note only two estimates for
140 single dosing were available across the dataset.

141

	log HR estimate	CI lower	CI upper	P
unvaccinated (reference)	0.625	0.413	0.838	< 0.0001
one dose	-0.300	-1.025	0.424	0.417
two doses	-0.421	-0.780	-0.063	0.021

142 **Table S3.** Meta-analytic model estimating the risk of Delta versus Alpha for hospitalisation
143 across the 5 studies included that estimated risk within vaccinated and unvaccinated
144 individuals.

	log HR estimate	CI lower	CI upper	P
unvaccinated (reference)	0.596	0.231	0.961	0.001
vaccinated	-0.388	-0.721	-0.056	0.022

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146 **Table S4.** Meta-analytic model estimating the risk of Delta versus Alpha for hospitalisation
147 across the 5 studies included that estimated risk within the vaccinated and unvaccinated
148 individuals, separated by vaccination dose. Note only two estimates for single dosing were
149 available across the dataset.

	log HR estimate	CI lower	CI upper	P
unvaccinated (reference)	0.598	0.232	0.963	0.001
one dose	-0.295	-1.021	0.432	0.427
two doses	-0.410	-0.775	-0.045	0.028

150

151 **Table S5.** Meta-analytic model estimating the risk of Delta versus Alpha for hospitalisation
152 across the 2 studies that estimated the risk of Alpha compared to Wildtype variant in
153 vaccinated and unvaccinated individuals.

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	log HR estimate	CI lower	CI upper	P
unvaccinated (reference)	0.360	0.229	0.490	< 0.0001
vaccinated	-0.403	-0.895	0.089	0.108

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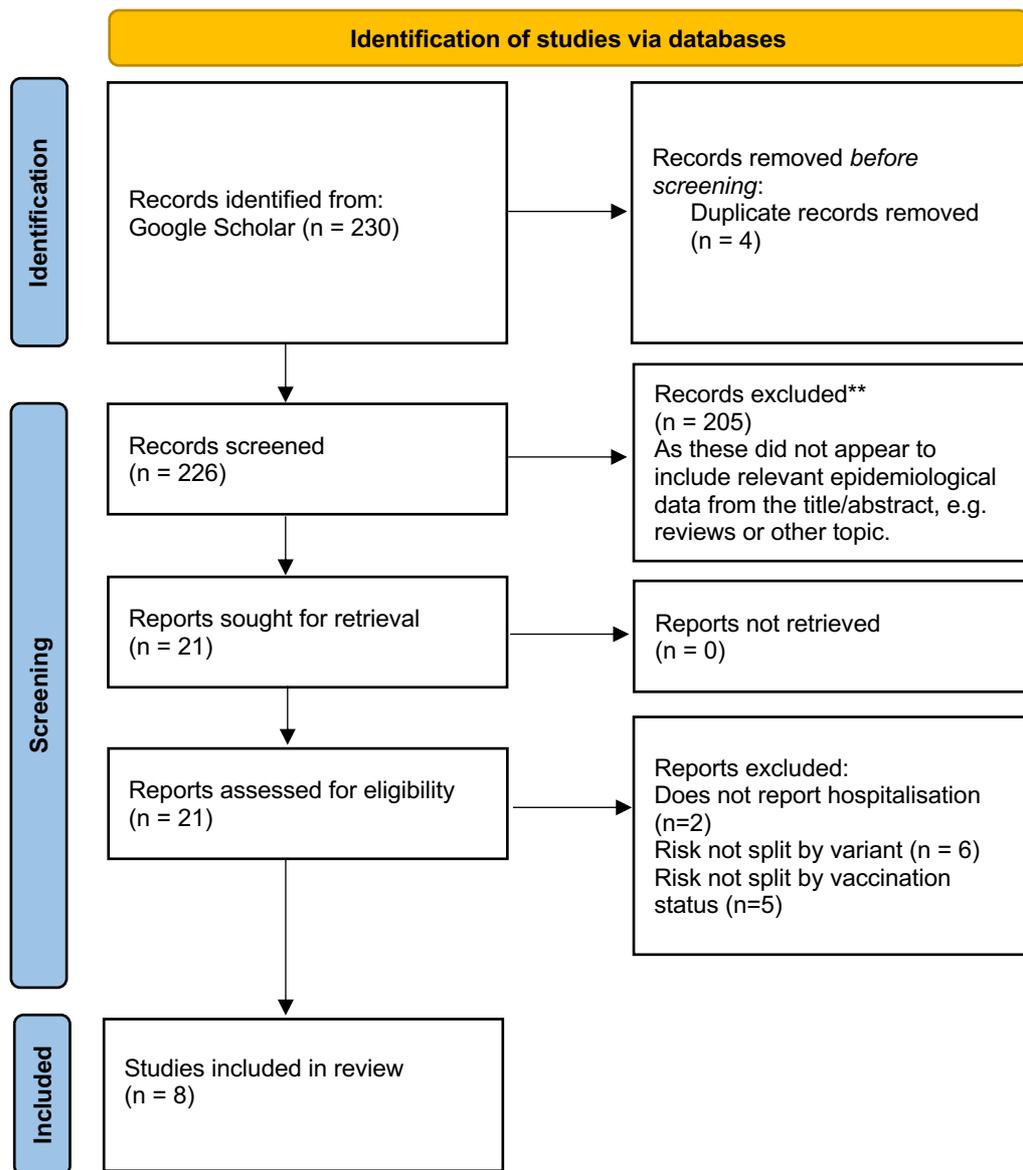
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202 **Supplementary Figure 1.** PRISMA Flow diagram of the literature search conducted.



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