Single Technology Appraisal

Nirmatrelvir plus ritonavir for treating COVID-19 (Partial Rapid Review of TA878) [ID6262]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nirmatrelvir plus ritonavir for treating COVID-19 (Partial Rapid Review of TA878) [ID6262]

Contents:

The following documents are made available to stakeholders:

Link to TA878 Casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19

1. **Additional data** submitted by Pfizer

2. **Therapeutics Clinical Review Panel (TCRP) modelling group findings** by Edmunds *et al*.

3. **External Assessment Group critique of the company data** prepared by the School of Health and Related Research (ScHARR)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Therapeutics for people with COVID-19 [ID4038]

NICE additional data requests

The NICE technical team have requested that Pfizer provide the follow clinical evidence to run a scenario analysis modelling by specific age groups in the mild COVID 19 setting (community setting):

1. Baseline characteristics for over 70s (including vaccination status, number of comorbidities)
2. Baseline/overall hospitalisation rates for untreated over 70s
3. Baseline/overall mortality rates for untreated over 70s
4. Treatment specific (nirmatrelvir plus ritonavir) hospitalisation and mortality rates for over 70s
5. Relative treatment effect of nirmatrelvir plus ritonavir (versus untreated/ standard care) in terms of hospitalisation and mortality rates for over 70s
    a. Hospitalisation or death relative risk
    b. All-cause mortality relative risk at 28 days

The NICE team have suggested that the evidence could come from EPIC-HR and EPIC-SR (vaccinated group), Open SAFELY or PANORAMIC. If data for the 70+ age group was unavailable, the NICE team have also agreed that data from similar age groups (e.g. 65+) would be considered as a suitable alternative. In line with NICE's requests, herein we present data for the 70+ population where available.

Based on available evidence, however, we believe this age threshold (i.e., 70+) may be overly conservative given the considerable risk of severe COVID-19 illness and COVID-19-related death at earlier ages (e.g., 60+ and 65+). Further, younger individuals with certain underlying comorbid conditions are at heightened risk for severe COVID-19 and also represent a group for which QALY loss is significant. Thus, in addition to age-based recommendations for the elderly, younger individuals with underlying comorbid illness would benefit from treatment to reduce the risk of progressing to severe COVID-19. Cost-effectiveness analysis can be used to determine an age threshold for inclusion in the recommendation. As such, we present a range of cost-effectiveness analyses. Based on the totality of evidence, we suggest the ***clinically appropriate and cost-effective 'base case' model is making Paxlovid available for all individuals aged 60+ (age-based) and those 18–59-year-olds with at least one risk condition as defined by PANORAMIC (risk based)***. This approach ensures equitable access to treatment across age groups indicated for Paxlovid based on their risk of COVID-19 severe disease outcomes. Similar recommendations have been made for influenza antiviral treatments which were assessed and recommended by NICE to patients with at list one risk factor and all those aged over 65 (TA158 and TA168) and is aligned with the JCVI risk groups for prioritization of influenza vaccination. It should be noted that influenza has similar risk factors for severe disease to COVID-19.

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NICE additional data requests

Baseline hospitalisation rates and mortality rates

PANORAMIC clinical trial data

Please note that this data has been supplied directly from the PANORAMIC group and should be treated as **Academic in Confidence.** Age stratified hospitalisation rates and mortality rates have been supplied by the PANORAMIC study investigators to reflect hospitalisation rates and mortality rates in alternative high-risk definition populations which combine pre-existing risk conditions with a high age threshold by restricting the patient population to those with baseline age between 55+ and 75+ years. This data is derived from the placebo arm of the PANORAMIC Molnupiravir trial to reflect hospitalisation rates in the age stratified untreated population during the omicron variant era (December 2021 to April 2022).

Table 4. Age stratified hospitalisation and mortality data from the placebo arm of the PANORAMIC Molnupiravir trial. Source: PANORAMIC study

Population	Baseline hospitalisation rate	Baseline 28-day Mortality rate	Mean age not hospitalised (years)	Mean age hospitalised (years)
All aged 50+ and 18–49 year olds with ≥1 pre-existing high risk health condition^	[redacted]	[redacted]	[redacted]	[redacted]
All aged 55+ and 18–54 year olds with ≥1 pre-existing high risk health condition^	[redacted]	[redacted]	[redacted]	[redacted]
All aged 60+ and 18–59 year olds with ≥1 pre-existing high risk health condition^	[redacted]	[redacted]	[redacted]	[redacted]
All aged 65+ and 18–64 year olds with ≥1 pre-existing high risk health condition^	[redacted]	[redacted]	[redacted]	[redacted]
All aged 70+ and 18–69 year olds with ≥1 pre-existing high risk health condition^	[redacted]	[redacted]	[redacted]	[redacted]
All aged 75+ and 18–74 year olds with ≥1 pre-existing high risk health condition^	[redacted]	[redacted]	[redacted]	[redacted]
^ health risk condition as defined by the PANORAMIC clinical trial eligibility criteria				

It should be noted that after clinical guidance was issued to allow priority access to treatment for a subgroup of high-risk patients who were identified by the McInnes report as at “highest risk”, the PANORAMIC clinical trial excluded this group from their recruitment. The hospitalization and mortality rates from the trial therefore

underestimates the true rates for the considered population. This is readily demonstrated by comparing the hospitalization and mortality rates of the 65+ and 75+ populations in PANORAMIC (Table 5) to the UK Gov Coronavirus dashboard and NHS COVID-19 hospital activity statistics,(1, 2) which show hospitalization rates of 6.5% in the 65+ population and 10.9% in the 75+ population. Further details are in the next section.

Despite underestimating the true hospitalization and mortality rates for the considered population, the age-stratified PANORAMIC data presented in Table 4 and Table 5 clearly demonstrate an increase in risk of hospitalisation and mortality with older age. Additionally, the data confirms increasing risk when patients are further stratified to include those with pre-existing morbidity defined as a high-risk factor by the PANORAMIC inclusion criteria. Even when considering patients aged 60+, individuals are shown to be at a much greater risk of hospitalisation when compared to the full PANORAMIC cohort, even when not considering additional comorbidities (Hospitalisation rate: [redacted] vs. 0.77%, respectively). The rates are even greater still in the NICE requested population of 70+ (Hospitalisation rate: [redacted].

As noted in section 3,13 of the final draft guidance, it is important to consider that these hospitalisation rates from PANORAMIC are an underestimate, as the study inclusion criteria were not limited to the set of 'highest-risk' factors as in the McInnes study; therefore, the PANORAMIC study population had lower risk of severe disease than the McInnes defined high-risk population. This should be taken into consideration before applying any of this age stratified data alongside the McInnes derived 'high-risk' criteria being considered in this appraisal.

Table 5. Age stratified hospitalisation and mortality data from the placebo arm of the PANORAMIC Molnupiravir trial.

Source: PANORAMIC study
NB: Data is Academic in confidence

Population	Baseline hospitalization rate	Baseline 28-day Mortality rate	Mean age not hospitalised (years)	Mean age hospitalised (years)
All aged 55+	[redacted]	[redacted]	[redacted]	[redacted]
All aged 60+	[redacted]	[redacted]	[redacted]	[redacted]
All aged 65+	[redacted]	[redacted]	[redacted]	[redacted]
All aged 70+	[redacted]	[redacted]	[redacted]	[redacted]
All aged 75+	[redacted]	[redacted]	[redacted]	[redacted]
All aged 18+ with one pre-existing condition	[redacted]	[redacted]	[redacted]	[redacted]
All aged 55+ with one pre-existing condition	[redacted]	[redacted]	[redacted]	[redacted]
All aged 60+ with at least one pre-existing health condition	[redacted]	[redacted]	[redacted]	[redacted]
All aged 65+ with at least one pre-existing health condition	[redacted]	[redacted]	[redacted]	[redacted]

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All aged 70+ with at least one pre-existing health condition	[redacted]	[redacted]	[redacted]	[redacted]
All aged 75+ with at least one pre-existing health condition	[redacted]	[redacted]	[redacted]	[redacted]

NHS England data

Age stratified baseline hospitalisation and mortality data were also sourced from the UK Gov Coronavirus dashboard (incidence and 28-day mortality data) and NHS COVID-19 hospital activity statistics.(1, 2) These data are the most generalizable for the English population. Only data stratification for the 65+ and 75+ populations are available from the NHS sources and not stratified by pre-existing morbidity, hence only data for these populations are presented. Hospitalisation and mortality rates for untreated COVID positive individuals aged 65+ and 75+ are presented in Figure 1 and Figure 2, respectively. Datasets used to derive this data are uploaded alongside this document. The mean rates are calculated based on the period of January 2022 – March 2022, reflecting the omicron period up until the point when mass testing was ceased. Furthermore, this period also overlaps with the era of free mass COVID-19 testing which ended in England on 1 April 2022. This provides us with the most accurate incidence data to allow calculation of infection-hospitalization rates and infection-mortality rates. We also capture in the plots data from December 2021 to demonstrate the transition in hospitalization and mortality rates as variant predominance switched from delta to omicron. Based on this data, the mean infection related hospitalisation rate (corrected for hospitalizations specifically for COVID-19) is 6.5% in the 65+ population and 10.9% in the 75+ population. The mean infection related mortality rate (within 28 days of a positive COVID-19 test) is 2.7% in the 65+ population and 5.0% in 75+ population. This data confirms that PANORAMIC hospitalisation rates are underestimates and are more reflective of the broader at-risk population, not just those at the highest risk of severe disease.

In the draft final guidance, the proposed recommendation to keep treatment restricted to highest risk population who can already access (since December 2021) treatment though COVID medicine delivery units (CMDUs) does not address the health need of the whole population. For example, in January 2023, it is estimated that 5,824 patients were admitted to hospital for COVID-19(1). Of these patients, 45% (2,653) were over 65 years old despite this population making up only 18% of the population of England (3) (65+ presented due to restricted availability of age stratified data). This disproportionate impact on the older population highlights the need to provide access to a broader population beyond the current clinical guidance based on the McInnes population.

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NICE additional data requests

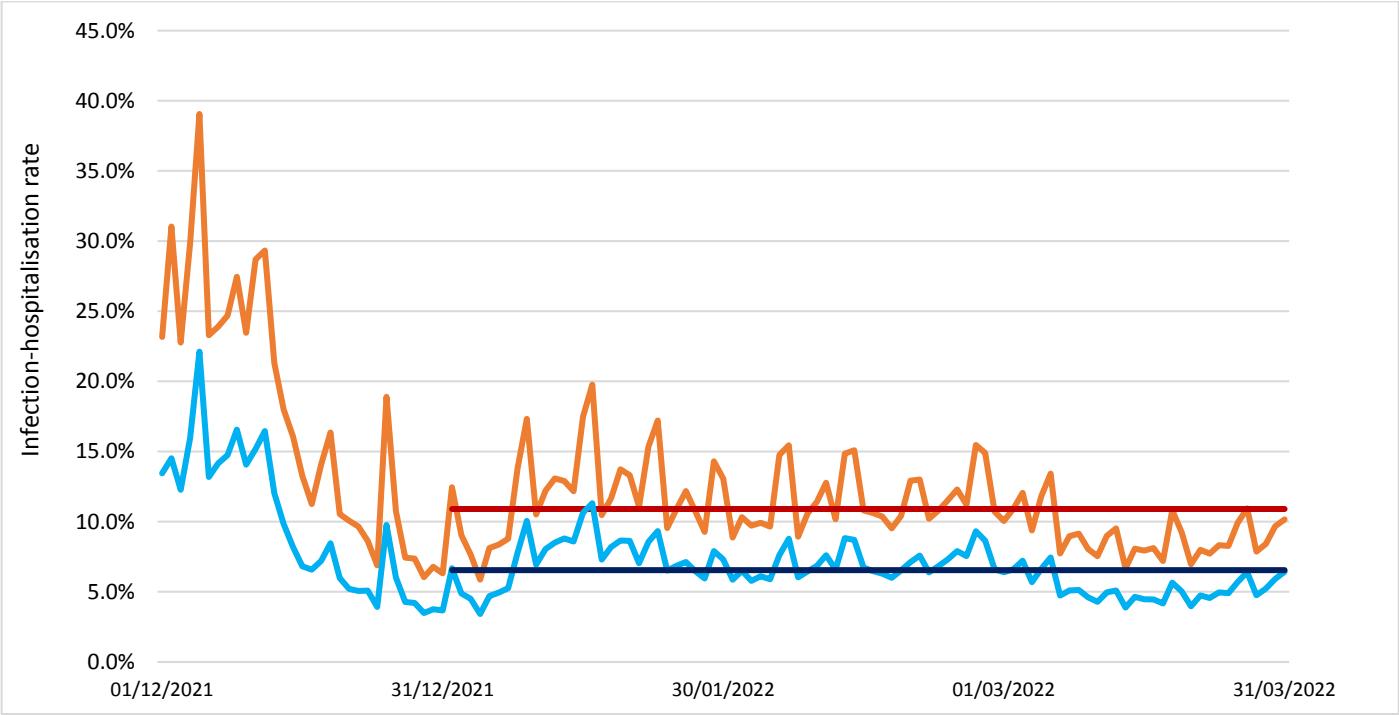

Figure 1. Infection-hospitalization rate corrected for hospitalization with COVID-19 in untreated individuals aged 65+ (blue) and 75+ (orange). Horizontal lines display the mean rate for the period 1 January 2022 to 31 March 2022. Source: UK Gov coronavirus dashboard and NHS COVID-19 hospital activity statistics(1, 2)

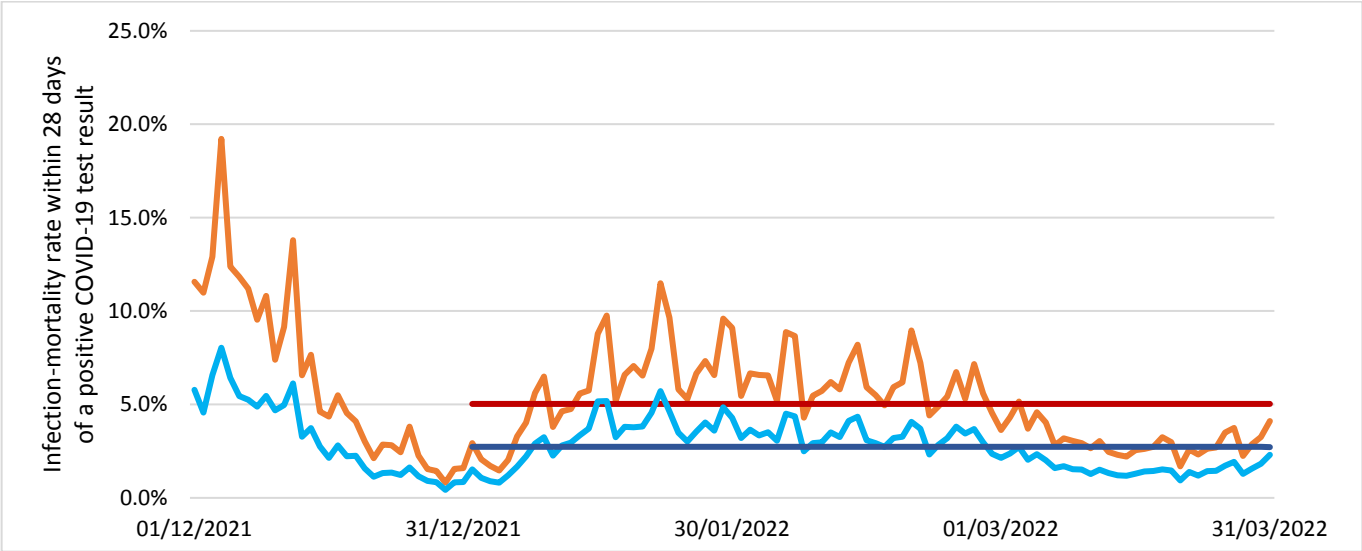

Figure 2. Infection-mortality rate within 28 days of a positive COVID-19 test in untreated individuals aged 65+ (blue) and 75+ (orange). Horizontal lines display the mean rate for the period 1 January 2022 to 31 March 2022. Source: UK Gov coronavirus dashboard and NHS COVID-19 hospital activity statistics(1, 2)

It should be noted that the hospitalisation data presented above is adjusted for hospitalisation specifically for COVID-19. Data for patients testing positive in the community setting and admitted due to COVID complications

specifically is most relevant to this appraisal; however, consideration should also be given to this broader group due to the confounding nature of COVID-19 infection co-occurring with other illness and subsequent mortality. Additionally, it was raised during the second appraisal meeting that patients testing positive incidentally once hospitalised for other reasons are difficult to capture but should be considered, nonetheless.

Treatment specific Hospitalisation and Mortality rates and relative treatment effect: EPIC-HR subgroup analysis

To provide data on the relative treatment effect of Paxlovid, data was sourced from EPIC-HR analyses for patients in the following age categories: Full trial (18-59 with at least one pre-existing health condition and all 60+), 60+, 65+ and 70+ (Table 6). Data represents the relative risk reduction of COVID-19 related hospitalisation and all-cause mortality within 28 days for patients treated with Paxlovid. The efficacy of Paxlovid in preventing a hospitalisation or death increases with age and all relative risk reduction % for the 60+, 65+ and 70+ populations are above the mean Paxlovid efficacy values of the full EPIC-HR trial.

Table 6. Relative risk of COVID-19 related hospitalisation, day 28 all all-cause mortality and hospitalisation or death from EPIC-HR trial. Data presented are for the age stratified population. Source: Pfizer EPIC-HR study

Trial	Population	Paxlovid		Placebo		Treatment specific rates	Relative Risk Reduction vs Placebo	Treatment specific rates	Relative Risk Reduction vs Placebo
		Hospitalisation	Death	Hospitalisation	Death	COVID-19-Related-Hospitalization %	COVID-19-Related-Hospitalization %, (95%CI)	Death from any cause through day 28 %	Death from any cause through day 28 %, (95%CI)
EPIC HR	Full trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	65+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EPIC-SR clinical trial and Paxlovid treatment in the vaccinated population during omicron era

EPIC-SR has not been included here as the study was not powered for the secondary endpoint of hospitalisation and death and event rates were very low. To maintain alignment with previous model inputs, we have provided additional data from EPIC-HR above.

Consistent with the EPIC trial results are real-world data that extend the evidence on clinical effectiveness of Paxlovid to the Omicron-dominant period, including BA.1, BA.2, and BA.4/5, and to the vaccinated and boosted patient population at high risk for progression to severe COVID-19. Published evidence from Israel, Hong Kong, Canada, and the United States show that Paxlovid is effective in reducing the risk of hospitalization or death from COVID-19 under real-world use. However, limited data are available that report Paxlovid effectiveness stratified

according to both age group and COVID-19 vaccination status. One study, conducted by the US Centers for Disease Control and Prevention, examined subgroups defined by both age group and vaccination status, and found that Paxlovid treatment within five days of diagnosis was effective against COVID-19 hospitalization among patients aged 50-64 years and aged ≥65 years across vaccination status (unvaccinated, vaccinated with 2 mRNA doses, and vaccinated with ≥3 mRNA doses) (4). In studies that reported effectiveness separately for age group and vaccination status, Paxlovid was effective against hospitalization or death among adults aged ≥60 years (5, 6), ≥65 years (7, 8), and ≥70 years (9), and Paxlovid was effective among vaccinated patients (8, 9) or effectiveness did not vary according to vaccination status (6, 7) (5).

It is important to highlight that these six studies did not have data describing the date of symptom onset and could not account for time between symptom onset and treatment initiation in the evaluation of Paxlovid effectiveness against hospitalization or death. In the only study with such data, Paxlovid had high effectiveness across vaccination status, and earlier treatment was associated with increased clinical benefit. This US healthcare database study (10) (now accepted at Lancet Infectious Diseases) reported 80% effectiveness among all patients, 83% among patients vaccinated with ≥2 COVID-19 vaccine doses, and 92% among patients vaccinated with ≥3 COVID-19 vaccine doses, when patients were treated within 5 days of symptom onset (median time from symptom onset to testing = 2 days). Moreover, effectiveness increased (from 80%) to 90% when patients were dispensed treatment on the same day as testing. In contrast, when treatment was dispensed at any time regardless of symptom timing, effectiveness was moderate, at 54% among all patients, 55% among patients vaccinated with ≥2 COVID-19 vaccine doses, and 67% among patients vaccinated with ≥3 COVID-19 vaccine doses.

As noted in the final draft guidance, there is no evidence of decreased in-vitro efficacy of Paxlovid against different SARS-CoV-2 variants.

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NICE additional data requests

Baseline characteristics by age (vaccination status and number of comorbidities)

Vaccination status

Data on vaccine uptake stratified by age has been sourced from the UK Gov Coronavirus dashboard(11). The data presented here corresponds to the percentage of people in England who have received an autumn booster COVID-19 vaccination, by age group, for the 60+ population (Figure 3).(11) Autumn booster data is presented as this is the most relevant to patients' uptake and defence in the Omicron period. Please note that granular data inputs per age category are provided on the UK Gov dashboard. We also provide vaccination coverage for December 2021 to March 2022 (Table 7 and Figure 4) which is the same period as that of the data used to estimate population hospitalization and mortality rates in Figures 1 and Figure 2.

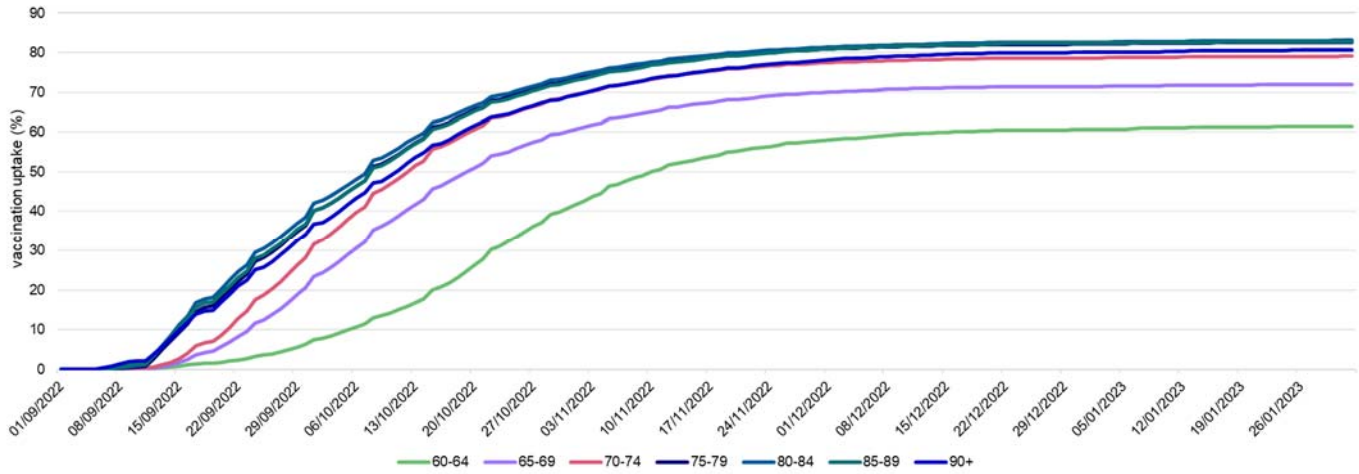
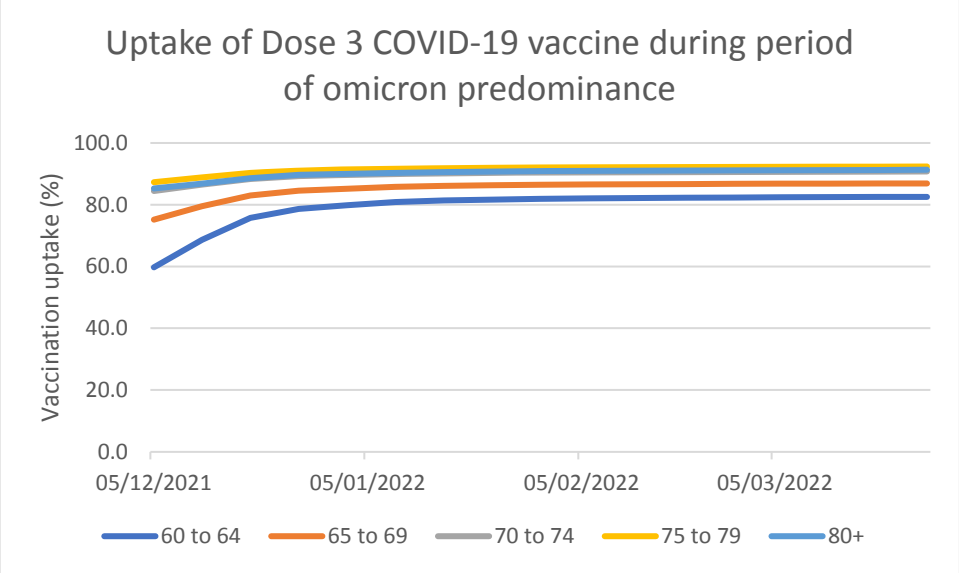


Figure 3. Uptake of Autumn booster COVID-19 vaccination by age group (60+) for September 2022 to January 2023. Source: UK Gov Coronavirus dashboard(11)

Table 1: Coverage by vaccine status (dose 1, 2 and 3) during the period of omicron predominance in December 2021 (up to week 50 data 2021) and March 2022 (up to week 12 data 2022).

Age group	Vaccinated with at least 1 dose (%)		Vaccinated with at least 2 doses (%)		Vaccinated with at least 3 doses (%)	
	December 2021	March 2022	December 2021	March 2022	December 2021	March 2022
60–64	90.8	91.0	89.4	89.8	75.4	82.6
65–69	92.6	92.7	91.5	91.7	82.7	86.9
70–74	94.7	94.8	93.8	94.0	88.0	90.8
75–79	95.8	95.8	95.0	95.2	89.9	92.4
≥80	95.6	95.6	94.9	95.0	87.9	91.4

Figure 4: Uptake of dose 3 COVID-19 vaccination by age group (60+) during the period of omicron predominance Source: National flu and COVID-19 surveillance data report: 31 March 2022 (week 13)



Comorbidities

While age and pre-existing high risk health conditions are independent risk factor for severe COVID-19 outcomes, their combined effect seems to exacerbate severity of COVID-19 outcomes and therefore has an additive effect on the risk of hospitalization and mortality as shown in the PANORAMIC trial data (Table 5). This is also true for a combination of different pre-existing high risk health conditions in multi-morbid people which shows dose-response relationship with severe COVID-19 outcomes. The risk of severe COVID-19 outcomes increases with increasing number of underlying medical conditions (multi-morbidities) (Figure 5)(12). Even in the Omicron era, older age, frailty and multimorbidity remain significant risk factors for a worse clinical outcome (13-17). This matrix nature of the relationship between different risk factors and severe COVID-19 outcomes should be considered when defining a population at high risk and is the basis of tools such as the QCOVID risk calculator (18).

The prevalence of COVID-19 health risk conditions and multimorbidity is highest in the older population highlighting the need for inclusion of an age threshold as part of COVID-19 treatment recommendation. A study (19) (UKHSA in partnership with LSHTM) using CPRD dataset calculated the at-risk point prevalence for patients who were deemed at moderate and high risk of severe COVID-19 based on the national guidance earlier on in the pandemic (list of included condition available in appendix 1). The at-risk health conditions in this study are near identical to that of the PANORAMIC clinical trial. The data (Figure 6) shows an increase in prevalence of at-risk health conditions with age with at least 50% of over 65 years old having at least one of the conditions that places them at risk of severe COVID-19. It is well documented that age is positively correlated with the prevalence of co-morbidities,(20, 21) as well as the number of conditions an individual has (multi-morbidities)(21-24). Additional contemporary data informing the number of comorbidities for different age groups has been sourced from Kuan et al. 2023.(25). This study examined multimorbidity and comorbidity patterns stratified by age for 308 health conditions using electronic health records from individuals from CPRD linked to Hospital Episode Statistics (HES) admitted patient care dataset

in England. We have provided data for individuals older than 1 year and who had been registered for at least 1 year in a participating general practice during the study period (between April 1, 2010, and March 31, 2015). The data shows that the number of diagnosed conditions increases with age (Figure 7). This data along with the risk associated with age and the likelihood of being multimorbid is strong evidence for the need of an age threshold as part of COVID-19 treatment recommendation.

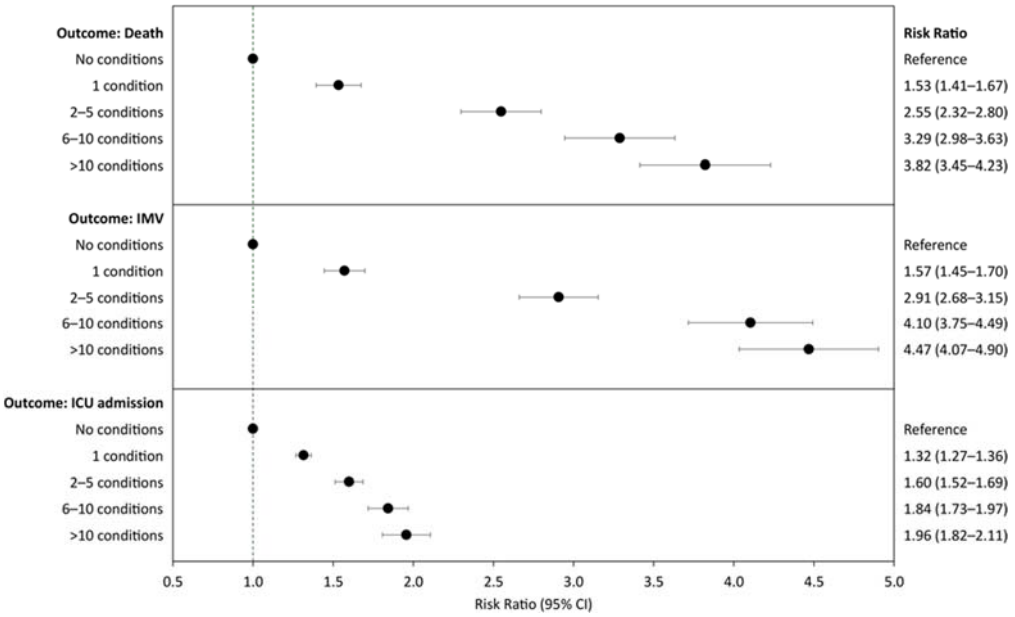


Figure 5. Risk ratio (95% CI) of death, invasive mechanical ventilation (IMV), and admission to intensive care unit (ICU), by the number of underlying medical conditions among adults hospitalized with COVID-19 in the Premier Healthcare Database Special COVID-19 Release. *Each panel contains the results of a single generalized linear model with Poisson distribution and log link function, adjusted for age group, sex, race/ethnicity, payer type, hospital urbanicity, US Census region of hospital, admission month, and admission month squared as controls. Patients who died without ICU care or IMV were excluded from the sample when estimating the model with the outcome of ICU care or IMV, respectively. Source: Kompaniyets et al. (2021)(12)*

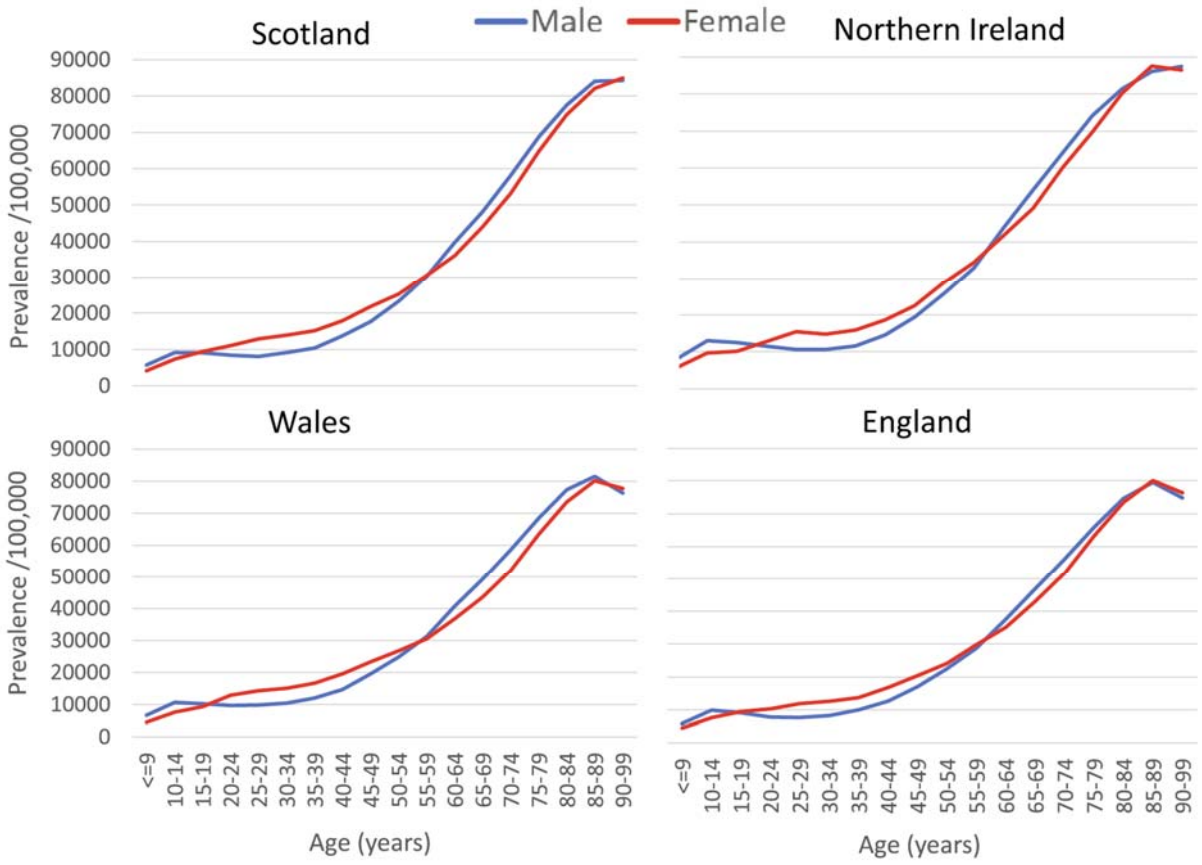


Figure 6: 2019-point prevalence of the at-risk population (COVID-19 specific high risk health conditions) by age and sex across the UK, N=2,706,053. Source Walker et al 2021 (19)

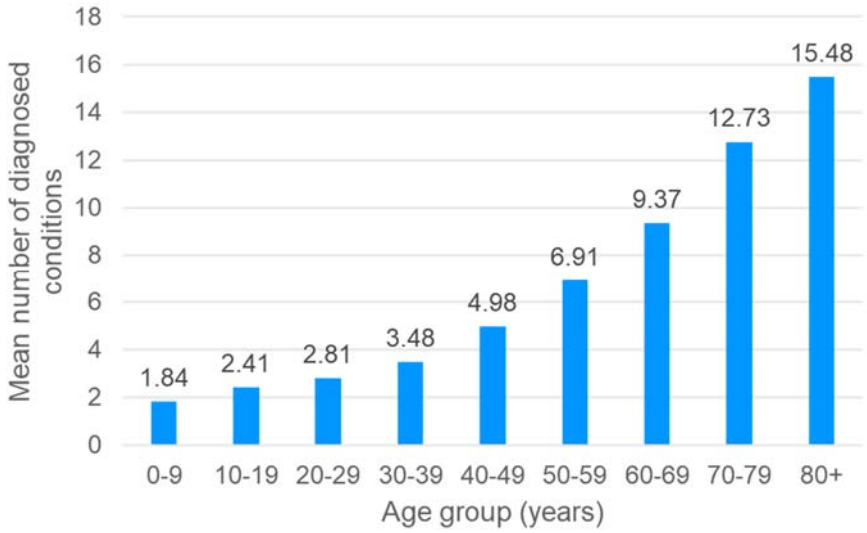


Figure 7. Number of diagnosed conditions stratified by age.
Source: Kuan et al. (2023)(25)

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NICE additional data requests

Age as an independent risk factor

We note in the FDG Section 3.6 that the committee suggests 'age over 70 years is likely to be confounded by underlying conditions which could also contribute to increased risk of severe disease'. 'The committee concluded that the McInnes report's definition of high risk included the most robust evidence of people who have a high risk for progressing to severe COVID-19, and this did not include age as an independent risk factor.' Therefore, a summary of data showing age as an independent risk factor has been provided here. The data include hazard ratios for hospitalization and mortality after adjusting for other factors including pre-existing conditions. In addition, data presented here from PANORAMIC and NHS digital shows a clear increase in hospitalization rates and mortality rates with increasing age.

As noted in the final draft guidance, age is considered an independent risk factor for severe COVID-19. We welcome NICE's request for age stratified data and agree that cost effectiveness should be evaluated in the setting where age is included as a high-risk factor. In line with the company submission, we would like to re-emphasise that there is a wealth of contemporary evidence that demonstrates age is an independent risk factor, including data from the living risk prediction algorithm QCOVID, which has demonstrated the impact of increasing age on the risk of COVID-19 death (Figure 3) and hospitalisation (Figure 4)(26). It should be noted that the QCOVID study controlled for other covariates when calculating hazard ratios for age related risk; therefore, the data represents the impact of age on mortality and hospitalisation alone and is unlikely to be confounded by other factors or comorbidities.

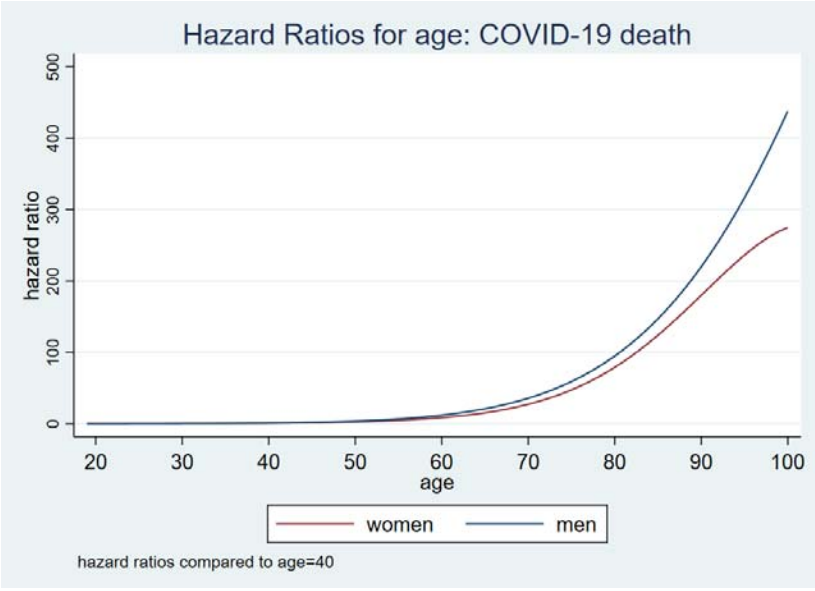

Figure 3. Adjusted hazard ratios for age and risk of COVID-19 deaths derived from the living risk prediction algorithm QCOVID(26)

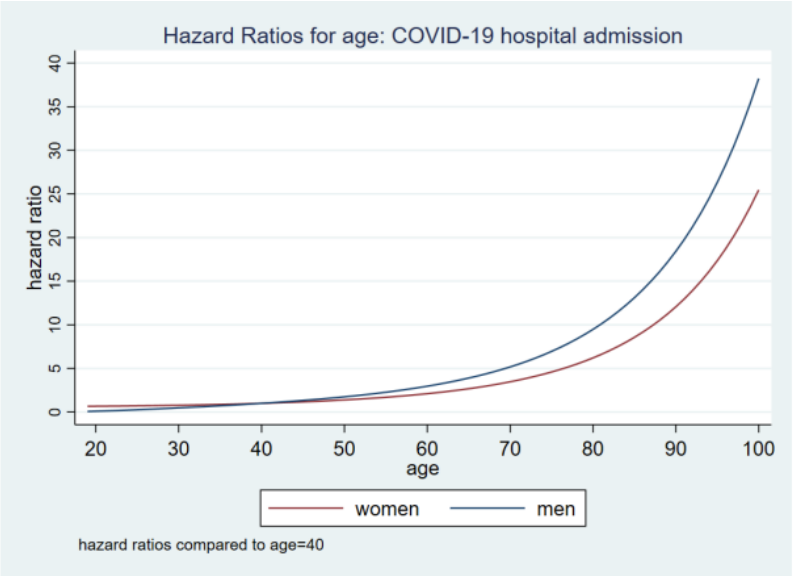

Figure 4. Adjusted hazard ratios for age and risk of COVID-19 hospitalisation derived from the living risk prediction algorithm QCOVID[26]

The NICE team indicated that the choice of 70+ as the threshold for 'high-risk' was based on discussions with clinical experts and committee members. We would like to emphasise that data presented during the company submission demonstrates that there is a substantially elevated risk well below this threshold, as low as in patients aged 50+: data from the QCOVID risk prediction tools(18, 26, 27) and the ISARIC report(28) demonstrate that the risk of death due to COVID-19 in patients aged 50+ is at least comparable to the 'high-risk' populations already included in the McInnes criteria (Figure 5), which continues to increase among older subgroups.

Figure 3 also compares data from the QCOVID3(27) and QCOVID4(18) risk prediction tools. QCOVID3 describes data from patients with between one and two doses of the COVID-19 vaccine between December 2020 and June 2021, whereas QCOVID4 describes data from a more contemporary patient cohort of mixed vaccine status, recruited during the Omicron wave in England. Whilst relative risk of each factor is shown to fluctuate slightly between the two populations, due to the differences in vaccination status and COVID variants, it is apparent that populations that were at an elevated risk due to COVID-19 earlier in the pandemic are still at an elevated risk during the omicron wave. Older age (>50 years) still poses a substantially greater risk than other factors during the omicron wave.

Therapeutics for people with COVID-19 [ID4038]

NICE additional data requests

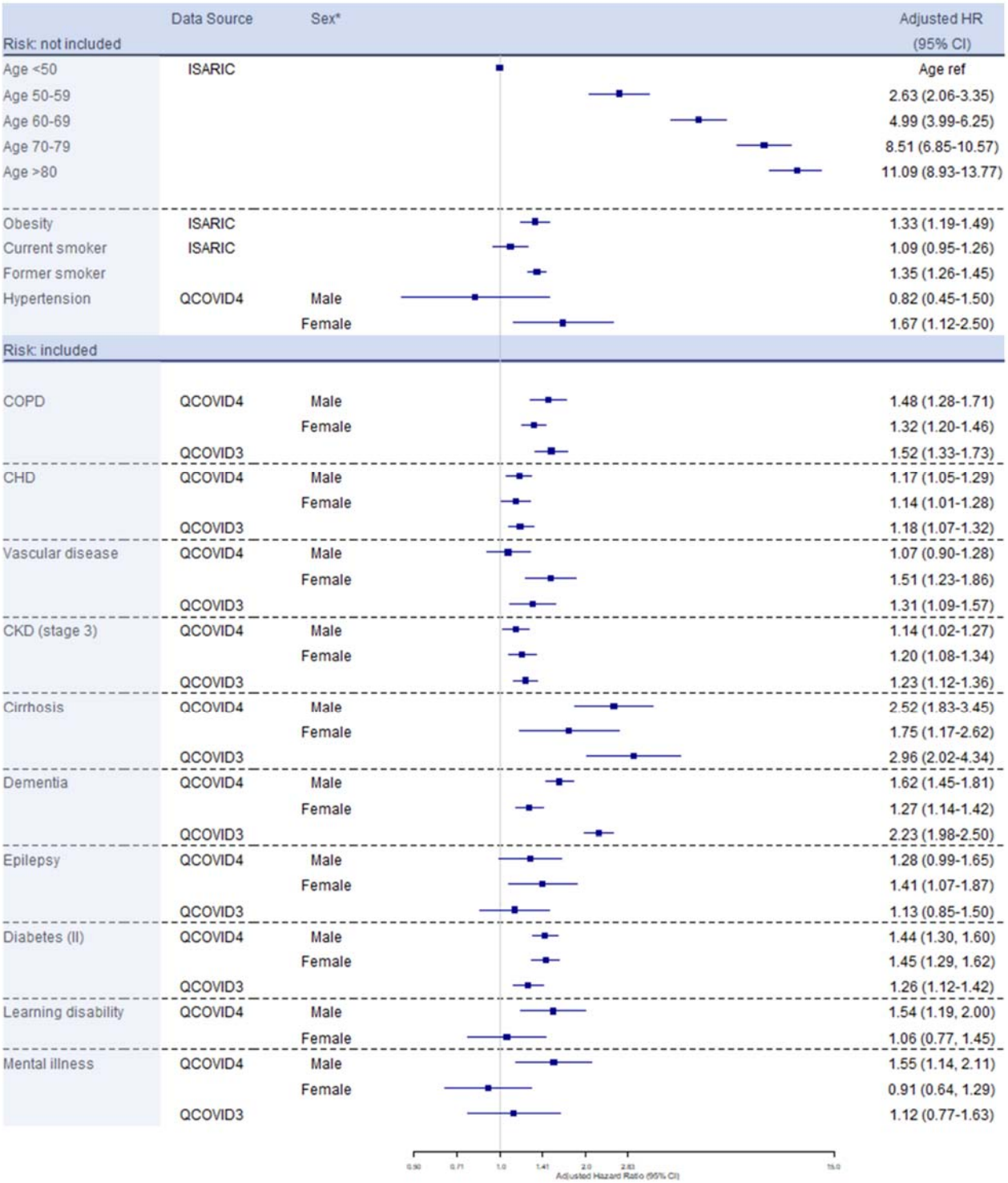

Figure 5. Risk of death due to COVID-19 in at-risk populations (Figure created using data from QCOVID and ISARIC studies).

* Risk data modelled separately for Males and Females in QCOVID

NICE National Institute for Health and Care Excellence

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NICE additional data requests

Summary of key model inputs

In brief, the data informing baseline hospitalisation rates and mortality rates representative of the population in England are derived from age-stratified NHS digital and the UK coronavirus dashboard. Further data from a subset of the population of the UK are derived from the PANORAMIC trial placebo arm of the recent Molnupiravir study. This PANORAMIC data **underestimates** baseline hospitalisation and mortality rates of the full population at risk of severe COVID-19 disease as it excludes the highest risk population who can already access treatment though COVID medicine delivery units (CMDUs). Relative treatment effects for Paxlovid were derived from EPIC-HR clinical trial data. Based on the list requested by NICE, we have summarised the key inputs that we suggest should inform the cost-effectiveness model for the age-based analyses (Table 1). We also flag a factual inaccuracy in the current EAG model, the relative risk of death from any cause through day 28 after treatment with Paxlovid is assumed to be 0.15 (0.001-0.63). It is unclear what the source of these values are as they are not in alignment with the EPIC-HR trial in which no deaths were observed in the treatment arm. We have therefore rectified this error. In addition to the requested data, we provide a table of proposed inputs as well as the cost-effectiveness analysis results in this document. Further detail and rationale for these data choices are given throughout this document.

NICE National Institute for Health and Care Excellence

Therapeutics for people with COVID-19 [ID4038]

NICE additional data requests

Table 2. Summary of suggested EPIC-HR modelling inputs to inform the age-based scenario analyses for Paxlovid by population

	Population				
Model input	**EAG base case McInnes**	**EAG base case PANORAMIC** (All ≥50 years and 18–49 years with ≥1 pre-existing high risk health condition^	All ≥60 years and 18–59 years with ≥1 pre-existing high risk health condition^	All ≥65 years and 18–64 years with ≥1 pre-existing high risk health condition^	All ≥70 years and 18–69 years with ≥1 pre-existing high risk health condition^
Baseline hospitalisation rates for untreated (%)	2.82%	0.77%	[redacted]	[redacted]	[redacted]
Mean Age (outpatient setting)	55	56.6	[redacted]	[redacted]	[redacted]
Relative risk* of death from any cause through day 28 (95% CI)	0.15 (0.001-0.63)	0.15 (0.001-0.63)	[redacted]	[redacted]	[redacted]
Relative risk* of hospitalisation or death (95% CI)	0.14 (0.07-0.27)	0.14 (0.07-0.27)	[redacted]	[redacted]	[redacted]

*Relative risk for Paxlovid vs. placebo

Data for baseline (untreated) hospitalisation rates are derived from the PANORAMIC study. Data for relative treatment effects are derived from EPIC-HR.

CI, confidence interval

^ health risk condition as defined by the PANORAMIC clinical trial eligibility criteria

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NICE additional data requests

Updated cost-effectiveness analysis

Using the latest EAG model, we performed cost-effectiveness analyses of Paxlovid using different baseline inputs (Table 1) from the PANORAMIC clinical trial and EPIC-HR clinical trial. We explored 4 different high-risk population definitions based on the PANORAMIC trial eligibility criteria:

(a) All individuals aged 50+ and 18-49-year-olds with at least one pre-existing high risk health condition as defined in the PANORAMIC trial (original EAG base case for PANORAMIC using rectified mortality efficacy),

(b) All individuals aged 60+ and 18-59-year-olds with one pre-existing health condition as defined in the PANORAMIC trial,

(c) All individuals aged 65+ and 18–64-year-olds with at least one pre-existing high risk health condition as defined in the PANORAMIC trial,

(d) All individuals 70+ and 18–69-year-olds with at least one pre-existing high risk health condition as defined in the PANORAMIC trial.

As noted in section 3,13 of the final draft guidance, it is important to consider that the hospitalisation rates from PANORAMIC are likely a conservative estimate in this appraisal, as the PANORAMIC trial did not include individuals with the 'highest-risk' factors (as defined in the McInnes study). Furthermore, we did not account for increased risk of baseline mortality with age as observed in the data. This analysis therefore takes a highly conservative approach. It should also be noted that we rectified a factual inaccuracy in the EAG model inputs. Specifically, we corrected the relative risk of death from any cause through day 28 after treatment with Paxlovid. The original assumption was 0.15 (0.001-0.63), however, no deaths were observed in the EPIC-HR Paxlovid treatment arm—thus we assumed 100% efficacy against this endpoint.

At high and mean (base case) efficacy, we find that Paxlovid is cost-effective at £30,000 per quality-adjusted life year (QALY) in all scenarios. At low efficacy, we find that Paxlovid is cost-effective at £30,000/QALY in a population of 18–59-year-olds with at least one pre-existing health condition as defined in the PANORAMIC trial and all aged 60+. Given cost-effectiveness observed at a 60+ threshold, not surprisingly, Paxlovid use also remained cost-effective at £30,000/QALY at higher age thresholds (i.e., in all 65+ and 18–64-year-olds with at least one pre-existing health condition as defined in the PANORAMIC trial; and in all 70+ and 18–69-year-olds with at least one pre-existing health condition as defined in the PANORAMIC trial [Table 2]).

Paxlovid was even more cost-effective at £30,000/QALY across all considered high risk definition scenarios and efficacy levels when more appropriate administration costs were applied (Table 3). The proposed cost of £117 accounts for both (1) the administration costs for PAXLOVID in primary care, and (2) the costs of medical review that is required to assess drug-drug interactions. The rationale for this preferred administration cost has been described previously during the company ACD response, but in brief:

The future delivery of treatments will be in a primary care setting and therefore we believe that applying the COVID-19 Medicine Delivery Unit (CMDU) deployment costs (£410) for Paxlovid is an overestimation compared to the likely real-world/business as usual costs once final guidance is implemented. A scenario representing the more complex

medical review required for care home patients should be considered as a conservative alternative: PSSRU review for this scenario found that "the average cost per resident of the multi-professional medication review intervention was £117".(29) This scenario represents the most complex medical review process and should be considered as the upper limit for oral antiviral administration cost.

Table 2. Cost-effectiveness (ICER: cost/QALY) of Paxlovid at different baseline hospitalisation rates. Cost-effectiveness calculated using latest EAG model and hospitalisation rates based on age stratified PANORAMIC data. Inputs summary in Table 1 and assuming administration costs of £410

Hospitalisation rate	High efficacy	Mean efficacy	Low efficacy
0.77% PANORAMIC: All 50+ and 18–49 years old with one pre-existing health condition	£29,740	£30,839	£33,125
[redacted] PANORAMIC: All 60+ and 18–59 years old with at least one pre-existing health condition)	£25,305	£26,340	£28,493
[redacted] (PANORAMIC: All 65+ and 18–64 years old with at least one pre-existing health condition)	£22,888	£23,514	£28,521
[redacted] (PANORAMIC: All 70+ and 18–69 years old with at least one pre-existing health condition)	£21,524	£21,524	£21,524

Table 3. Cost-effectiveness (ICER: cost/QALY) of Paxlovid at different baseline hospitalisation rates. Cost-effectiveness calculated using latest EAG model and hospitalisation rates based on age stratified PANORAMIC data. Inputs summary in Table 1 and assuming administration costs of £117

Hospitalisation rate	High efficacy	Mean efficacy	Low efficacy
0.77% PANORAMIC: All 50+ and 18–49 years old with at least one pre-existing health condition	£ 21,888	£ 22,868	£ 24,904

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[redacted] PANORAMIC: All 60+ and 18–59 years old with at least one pre-existing health condition)	£ 18,501	£ 19,432	£ 21,367
[redacted] (PANORAMIC: All 65+ and 18–64 years old with at least one pre-existing health condition)	£ 16,533	£ 17,098	£ 21,614
[redacted] (PANORAMIC: All 70+ and 18–69 years old with at least one pre-existing health condition)	£ 15,486	£ 15,486	£ 15,486

In support of this lower age threshold, it should be noted that the Joint Committee on Vaccination and Immunisation (JCVI) routinely recommends access to vaccinations based on age as an eligibility criterion, including their recommendation for access to the COVID-19 vaccine for which patients aged 50+ are routinely used to define eligibility (30). The recommendations are also much more easily implemented, as patients are able to easily understand their risk and whether or not they are recommended to receive treatment. Based on the JCVI criteria, data from QCOVID and ISARIC which demonstrates elevated risk prior to age 70 (see document Appendix), demonstrated cost-effectiveness in younger age groups, and consistency with the inclusion criteria of EPIC-HR (the primary source of efficacy data for Paxlovid), we propose that all individuals aged 60+ and 18-59 year olds with at least one pre-existing health condition as defined in PANORAMIC v should serve as the 'base case' in a range of age based scenarios conducted and represent the most evidence-based recommendation for Paxlovid use in the United Kingdom.

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Appendix 1

List of health conditions included in the point prevalence analysis by Walker at el (19)

- have a lung condition that's not severe (such as asthma, chronic obstructive pulmonary disease, emphysema or bronchitis)
- have been told by a doctor they have a severe lung condition (such as cystic fibrosis, severe asthma or severe chronic obstructive pulmonary disease)
- have heart disease (such as heart failure)
- have diabetes
- have chronic kidney disease
- have liver disease (such as hepatitis)
- have a condition affecting the brain or nerves (such as Parkinson's disease, motor neurone disease, multiple sclerosis or cerebral palsy)
- have a condition that means they have a high risk of getting infections
- have a condition that means they have a very high risk of getting infections (such as SCID or sickle cell)
- have blood or bone marrow cancer (such as leukaemia, lymphoma or myeloma)
- are taking medicine that can affect the immune system (such as low doses of steroids)
- are taking medicine that makes them much more likely to get infections (such as high doses of steroids or immunosuppressant medicine)
- have had an organ transplant
- are having chemotherapy or antibody treatment for cancer, including immunotherapy
- are having an intense course of radiotherapy (radical radiotherapy) for lung cancer
- are having targeted cancer treatments that can affect the immune system (such as protein kinase inhibitors or PARP inhibitors)
- have had a bone marrow or stem cell transplant in the past 6 months, or are still taking immunosuppressant medicine
- are very obese (a BMI of 40 or above)
- Are pregnant
- have a serious heart condition and are pregnant

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TCRP Modelling Group Findings

John Edmunds[1], Sheikh Aziz[2], Ben Goldacre[3], Julia Hippisley-Cox[3], Laurie Tomlinson[1], Elizabeth Williamson[1]

[1]London School of Hygiene and Tropical Medicine

[2]University of Edinburgh

[3]University of Oxford

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Background

The Antivirals and Therapeutics Taskforce has been planning for the potential wider deployment of antivirals against COVID-19. As part of this work the Therapeutics Clinical Review Panel (TCRP) are required to consider whether there are further high-risk patient groups that could benefit from antiviral treatment. In particular, whether there are groups that have a risk that is at least as high as those that are already eligible for treatment. The list that are currently being targeted include:

- chromosomal disorders affecting the immune system, including Down's syndrome
- certain types of cancer or have received treatment for certain types of cancer
- sickle cell disease
- certain conditions affecting their blood
- chronic kidney disease (CKD) stage 4 or 5
- severe liver disease
- had an organ transplant
- certain autoimmune or inflammatory conditions (such as rheumatoid arthritis or inflammatory bowel disease)
- HIV or AIDS who have a weakened immune system
- inherited or acquired conditions affecting their immune system
- rare neurological conditions: multiple sclerosis, motor neurone disease, Huntington's disease or myasthenia gravis

This note is intended as a guide to whether there are other groups in the population who have an equal or higher risk of severe COVID-19 outcomes than those groups listed above. The methods used are crude and any groups identified through this process would require closer scrutiny to better understand their risk and to what extent this might be modified by improved access to antivirals and therapeutics.

Methods

The Modelling Group met to consider estimates of the risk of severe disease (hospitalisation and/or death) in different patient groups, using data from recent, large, representative UK studies. Recent in this sense meant studies performed after the widespread use of immunisation in the UK. Three studies were identified:

1. A retrospective cohort study of linked primary care and death data by the OpenSAFELY consortium [1]. This study considered the first three waves of COVID-19 in the UK, though the last of these (28th May – 14th Dec 2021) which was primarily caused by the Delta virus is considered here (n=18.7 million adults).
2. Agrawal et al. (2022) [2] undertook a prospective cohort study constructed via electronic linkage of primary care, PCR testing, vaccination, hospitalisation and mortality data in the UK (n = 30 million). The study was conducted over the period December 20th 2021 to February 28th 2022 encompassing the first wave of the Omicron variant.
3. Hippisley-Cox et al. (2022) [3] constructed a cohort of adults in England using the QResearch database. They were linked to individual-level national data on vaccination, high-risk patients prioritised for COVID-19 therapeutics, SARS-CoV testing results, hospitalisation data, cancer registries, cancer treatment and radiotherapy records as well as national deaths registries. There were 1.3 million patients with a positive SARS-CoV-2 test that occurred between the 11th December 2021 and the 31st March 2022. These would have been mostly infected by the Omicron variant.

To determine a threshold for risk we assessed the lowest high-risk condition from those given by the TCRP (above) then compared the risks of severe COVID-19 disease associated with other comorbid conditions from these cohort studies to see whether there were other groups with risks that were at least as high.

Results

Detailed results are given in the respective papers.

Relative risks

All three studies provide a measure of the relative risks of severe COVID-19 by risk groups. There are, however, significant differences between the studies, including differences in the outcomes (COVID-19 deaths in [1]; severe disease (COVID-19 related hospital admission or death) in the case of [2]; and hospitalisation and death separately in [3]), differences in timing and therefore dominant strain (Delta in [1] and Omicron in [2] and [3]]) and variables adjusted for in analysis including vaccination status, which was not adjusted for in [1]. Unsurprisingly, there are differences in the results of the papers with, for instance, the OpenSAFELY consortium [1], reporting significant increases in risk of death from COVID-19 in Asian and Black ethnic groups persisting into the 3rd (Delta) wave of COVID-19, but Agrawal et al. [2] finding no such elevated risks of severe disease in these ethnic groups during the fourth (Omicron) wave. Hippisley-Cox et al. [3] also find no elevated risk of death by ethic group during the Omicron wave, though some increases in the risk of hospitalisation, particularly in Pakistani and Bangladeshi ethnic groups. This example serves to illustrate some of the differences between the studies. There are also, however, clear similarities in the results of the three papers, with all three suggesting that the risk of severe disease or death from COVID-19 is strongly related to **increasing age** and **obesity** as well as **male gender**.

Figures 1 to 4 show the adjusted rate ratio / relative hazard of severe COVID-19 / death from these three studies where the comparison group is not having the condition if the reference group is not given.

The lowest high-risk condition from within the TCRP groups appears to be “certain autoimmune or inflammatory conditions (such as rheumatoid arthritis or inflammatory bowel disease)”. This category of patients roughly coincides with “rheumatoid arthritis / lupus / psoriasis” (OpenSAFELY) and rheumatoid arthritis or SLE in both Agrawal et al. [2] and Hippisley-Cox et al. [3] although the latter study assesses the risk of severe COVID-19 in patients with inflammatory bowel disease separately and finds this to be lower than in rheumatoid arthritis patients (see Figures 3 and 4). In all three studies these rheumatoid arthritis-related groups are at moderately increased risk of severe disease or death. To aid comparison with the other risk categories the estimated 95% CI on the adjusted rate / hazard ratio for severe COVID-19 in these patient groups are highlighted in Figures 1 to 4 with a blue shaded bar. This therefore indicates the lower end of the elevated risk categories given by the TCRP. Those conditions that appear to have support across at least two studies indicating that the risk of severe disease in this group is at least as high as in the groups already identified by the TCRP are highlighted in **bold**.

Of conditions not listed by TCRP as high risk, the OpenSAFELY consortium suggests that in wave 3, the hazard ratio of death from COVID-19 was higher for patients who were obese (35-39.9 kg per m^2 2.25 (95% CI 2.06 - 2.47) , 40+ kg per m^2 4.77 (95% CI 4.34 - 5.25), had chronic kidney disease Stage 3b (2.56 (95% CI 2.35 - 2.78)), had dementia (2.81 (95% CI 2.46 - 3.23)), other neurological disease (2.3 (95% CI 2.03 -2.59)), learning difficulties (3.95 (95% CIs 3.09 - 5.05)), and severe mental illness (2.36 (95% CI 2.02 - 2.74)) than it was for patients with rheumatoid arthritis / lupus / psoriasis (1.72 (95% CI 1.59 - 1.85).There is support from the other studies that patients with **dementia** or **obesity** are at least as high a risk as the rheumatoid arthritis containing group. There is no corresponding support from the other studies for the other higher risk groups identified here, though it should be mentioned that the other two studies do not subdivide CKD Stage 3 into Stage 3b and 3a.

Analysis of the results of Agrawal et al. [2] suggests that of those conditions not explicitly listed by the TCRP, then pulmonary hypertension and dementia appear to have higher relative risks of severe disease than rheumatoid arthritis or SLE patients. Specifically, in those who had received a booster dose of an mRNA derived vaccine the estimated adjusted rate ratio for severe COVID-19 for those with dementia was 2.65 (95% CI 2.54 - 2.77) and 2.84 (95% CI 2.63 - 3.07) for patients with pulmonary hypertension, compared with a rate ratio of 2.32 (95% CI 2.20 - 2.45) for those with rheumatoid arthritis or SLE (all comparisons are to those without the condition and after adjusting for non-clinical factors). As mentioned above the other studies also identify **dementia** patients as being at significantly higher risk. There is a weak signal from the other studies that pulmonary hypertension may be associated with elevated risk with Hippisley-Cox et al. [3] identifying that women with pulmonary hyptertension/fibrosis may be at a similar or higher risk of hospitalisation and death than women with rheumatoid arthritis or SLE (Figures 3 and 4). This association does not appear to hold for men. Although the OpenSAFELY study does not look at pulmonary hypertension specifically, patients with High blood pressure or diagnosed hypertension were not found to be at higher risk than rheumatoid arthritis/lupus/psoriasis patients in the OpenSAFELY analysis (Figure 1).

Hippisley-Cox et al. [3] suggest that both male and female patients with **Type 1 diabetes** are significantly more likely to be hospitalised or die following SARS-CoV-2 infection than those who have rheumatoid arthritis or SLE (Figures 3 ND 4). There is some support from the other studies that diabetics may be at increased risk, but it is not consistent. Agrawal et al. [2] suggests that Type 1 diabetes patients are at a similar risk to those with rheumatoid arthritis (Figure 2). The OpenSAFELY consortium do not distinguish between Types 1 and 2 diabetes, but do find that all groups of **diabetes** (controlled, uncontrolled, without recent Hb1ac measure) were at similar or elevated risk of severe disease in the third wave compared with the reference group (those with rheumatoid arthritis / lupus / psoriasis).

The results of the Hippisley-Cox et al. [3] study also suggests that patients taking oral steroids are at significantly increased risk of death or hospitalisation than those with Rheumatoid arthritis or SLE (Figure 3 and 4). Agrawal et al. [2] do not find this group to be at greater risk (Figure 2), though the OpenSAFELY consortium found that asthma patients on oral steroids had a similar risk of death during the third wave as the rheumatoid arthritis containing group (Figure 1). There is thus weak support from these studied that patients on **oral steroids** may be at increased risk.

Hippisley-Cox et al. [3] also find some inconsistent patterns by gender and by outcome that may require further investigation. For instance, they find that women with congestive heart failure or thromboembolism appear to be at significantly greater risk of death (Figure 3) but not hospitalisation (Figure 4) than women with rheumatoid arthritis or SLE, whereas men with these comorbid conditions do not appear to have an elevated risk of either hospitalisation or death compared with those with rheumatoid arthritis or SLE. Agrawal et al. lend some support to these observations and find that patients with **heart failure** are at a similar risk of severe COVID-19 as patients with the rheumatoid arthritis or SLE (Figure 2).

Absolute risk of severe disease

The above analysis looks at risk of severe COVID-19 given the presence/absence of individual clinical risk factors. However, to put the risk of these conditions in context and assess whether there are other groups in the population (e.g. age groups) who may be at higher risk it is necessary to compare the absolute risk of severe disease or death across all these different groups. The OpenSAFELY consortium [1] does just this, the results of which are presented in Figure 5, where for ease of comparison the estimated 95% CI of the absolute risk of COVID-19 death associated with rheumatoid arthritis, lupus or psoriasis is shown as a shaded blue bar. The figure demonstrates that during the third (Delta) wave the absolute risk of death from COVID-19 from individuals who were over 70 years of age without other comorbidities was significantly higher than that of a typical (age standardised) patient with rheumatoid arthritis, lupus or psoriasis. Namely, 1.48 (95% CIs 1.41-1.55) per person-years for individuals aged 70-79 years and 4.54 per 1000 person-years (95% CI 4.37 - 4.7) for 80+ years of age vs 1.04 per 1000 person-years (95% CI 0.96 -1.12) for rheumatoid arthritis, lupus and psoriasis patients.

Discussion

The risk groups as defined by the TCRP and the three studies are not identical. In addition, there are methodological, outcomes and clinical coding differences between the studies and although all three are large and UK-based the timing of the studies differ and the variables

controlled for in the analysis differ too. There are also likely some differences in the patient populations. Some variation in results would therefore be expected, as well as some difficulties in reading across to the high-risk groups defined by the TCRP. These difficulties are illustrated with the findings related to diabetes, in which all three studies point to an increase in risk for some categories of diabetic patients, but as the subcategories differ between the studies it is difficult to clearly ascertain which of these groups are at greatest risk and why. The findings presented here should be regarded as a crude indicator of which patient groups warrant further, in depth, assessments of their risk of severe COVID-19 disease.

It is also clear that there have been changes in risk over the course of the pandemic [1]. Further changes may have occurred since these studies concluded (in late 2021 or early 2022) or may occur into the future. Indeed, the OpenSAFELY analysis has recently been updated to include data from the Omicron wave, but as these results are not yet in the public domain, we restrict the analyses here to the latest publicly available data.

All three studies suggest that there are some clinical risk groups who may have similar or greater relative risk of severe disease than those listed by the TCRP (i.e. a higher risk than that associated with rheumatoid arthritis and similar autoimmune conditions). The patients groups with support from at least 2 independent analyses include, those who are obese, certain classes of diabetes patients, patients with dementia, and possibly those with heart failure or who are on oral steroids. There is also a longer list of groups of patients which were identified as being high risk in single studies only. All of these categories of patients should be investigated further to ascertain whether they do indeed have an elevated risk, whether there are subgroups within them who have higher/lower risks than the average, what may be the underlying mechanism driving these changes in risk, and to what extent this may be ameliorated by improved access to novel COVID-19 antivirals or therapeutics.

Apart from clinical risk factors, the studies also highlight the continuing importance of other demographic and social differences in risk, with increasing age, in particular, persisting as a major independent risk factor for severe COVID-19 outcomes.

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[3] Hippisley-Cox J, Khunti K, Sheikh A, Nguyen-Van-Tam JS, Coupland CAC. QCovid 4 - Predicting risk of death or hospitalisation from COVID-19 in adults testing positive for SARS-CoV-2 infection during the Omicron wave in England. MedRXiv (2022). doi: https://doi.org/10.1101/2022.08.13.22278733

Fig 1. OpenSAFELY Hazard ratio of death by demographic and socio-economic variables (left) and clinical conditions, (right) by COVID wave. The 95% CI on the hazard for rheumatoid arthritis, lupus and psoriasis In the third wave is highlighted with a blue shaded bar. Adapted from [1].

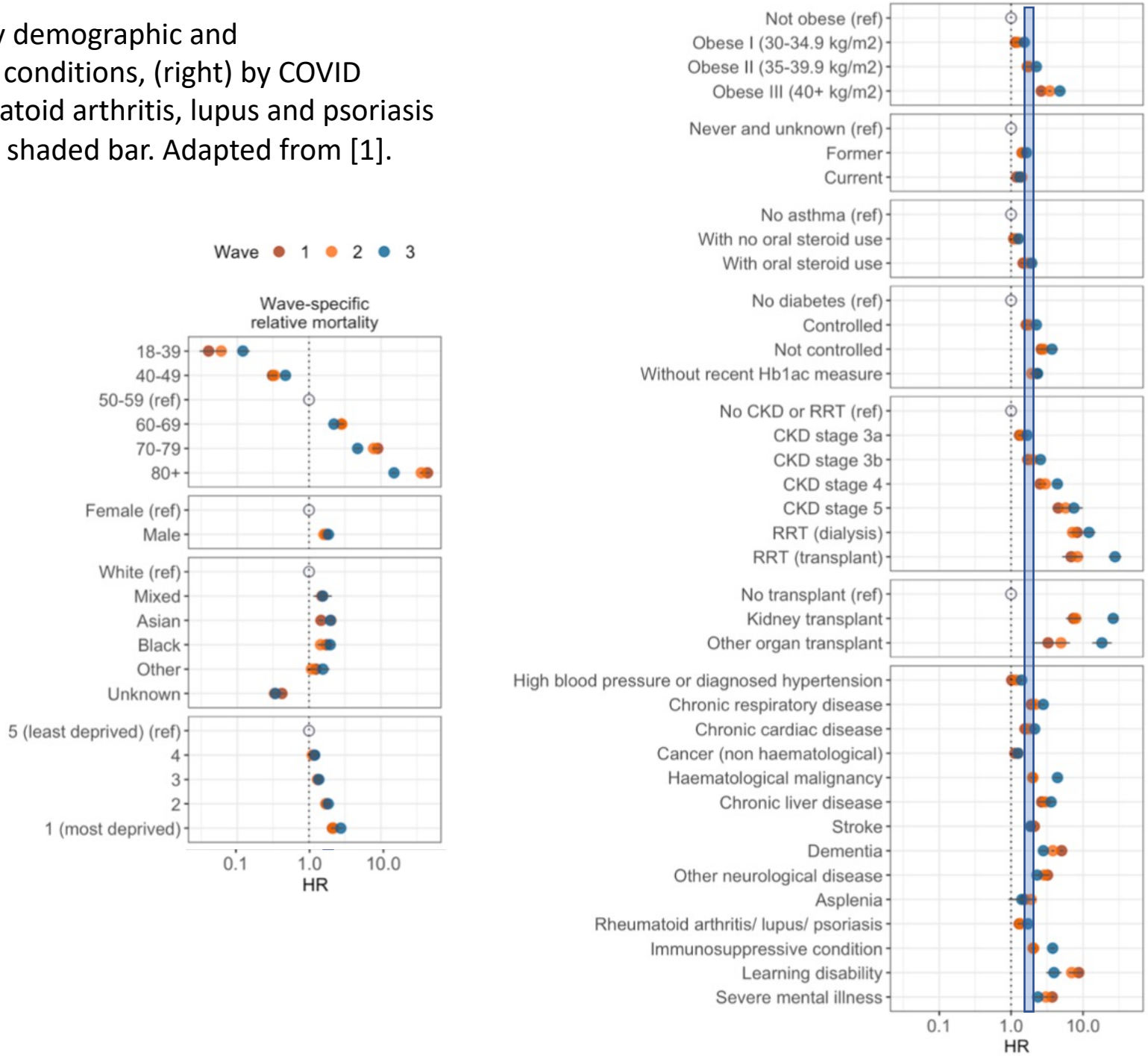


Figure 2. Adjusted rate ratios (95% confidence intervals) for specific clinical risk factors associated with COVID-19 hospitalisation or death, among individuals who received booster doses MRNA-1273 or BNT162b2. The 95% CI for the risk ratio associated with rheumatoid arthritis or SLE is highlighted with a blue shaded bar. Adapted from [2].

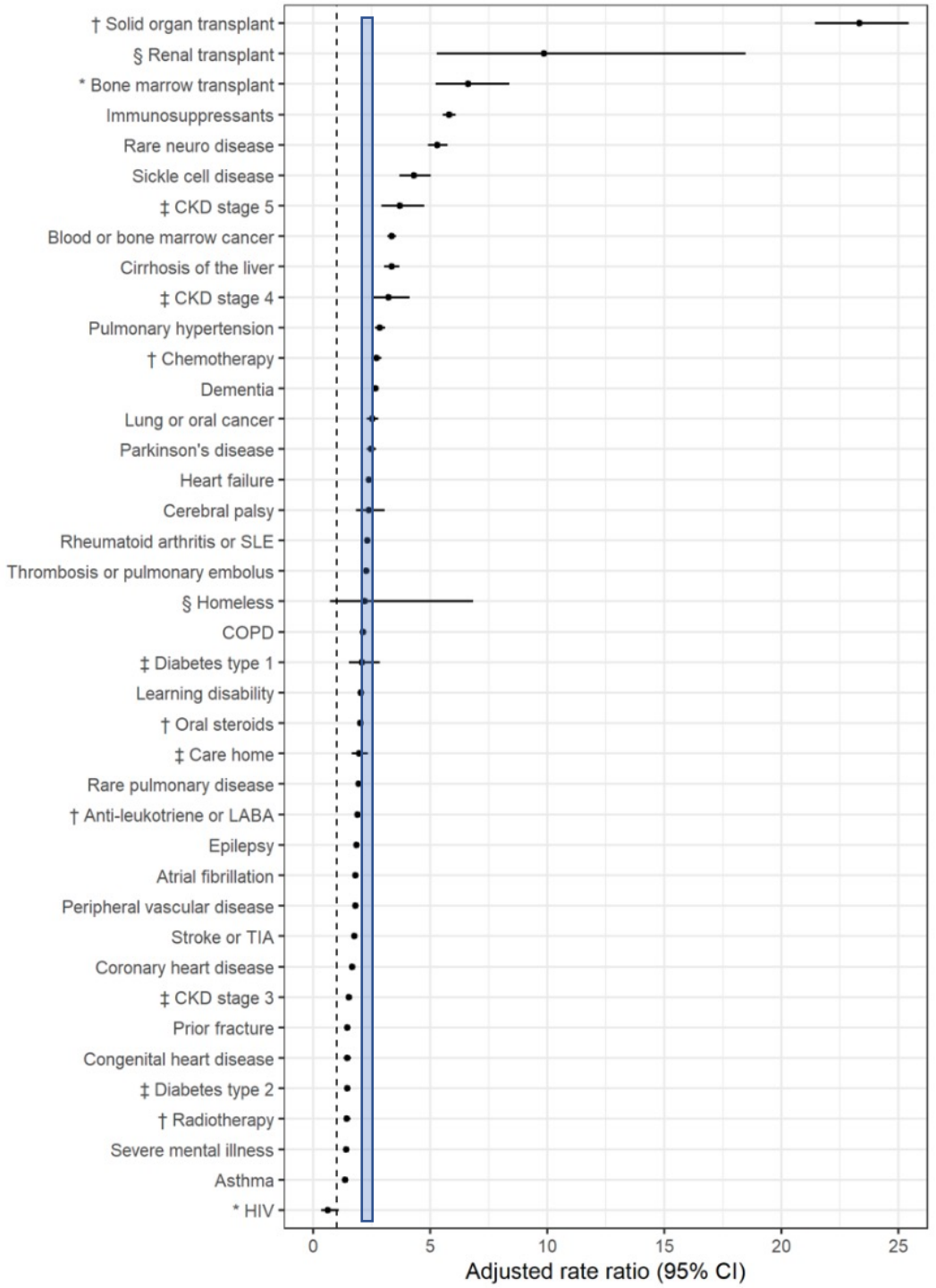


Figure 3. Adjusted hazard ratio of deaths by clinical risk groups for males (a) and females (b). Adjustment for all variables including age and BMI. Adapted from [3].

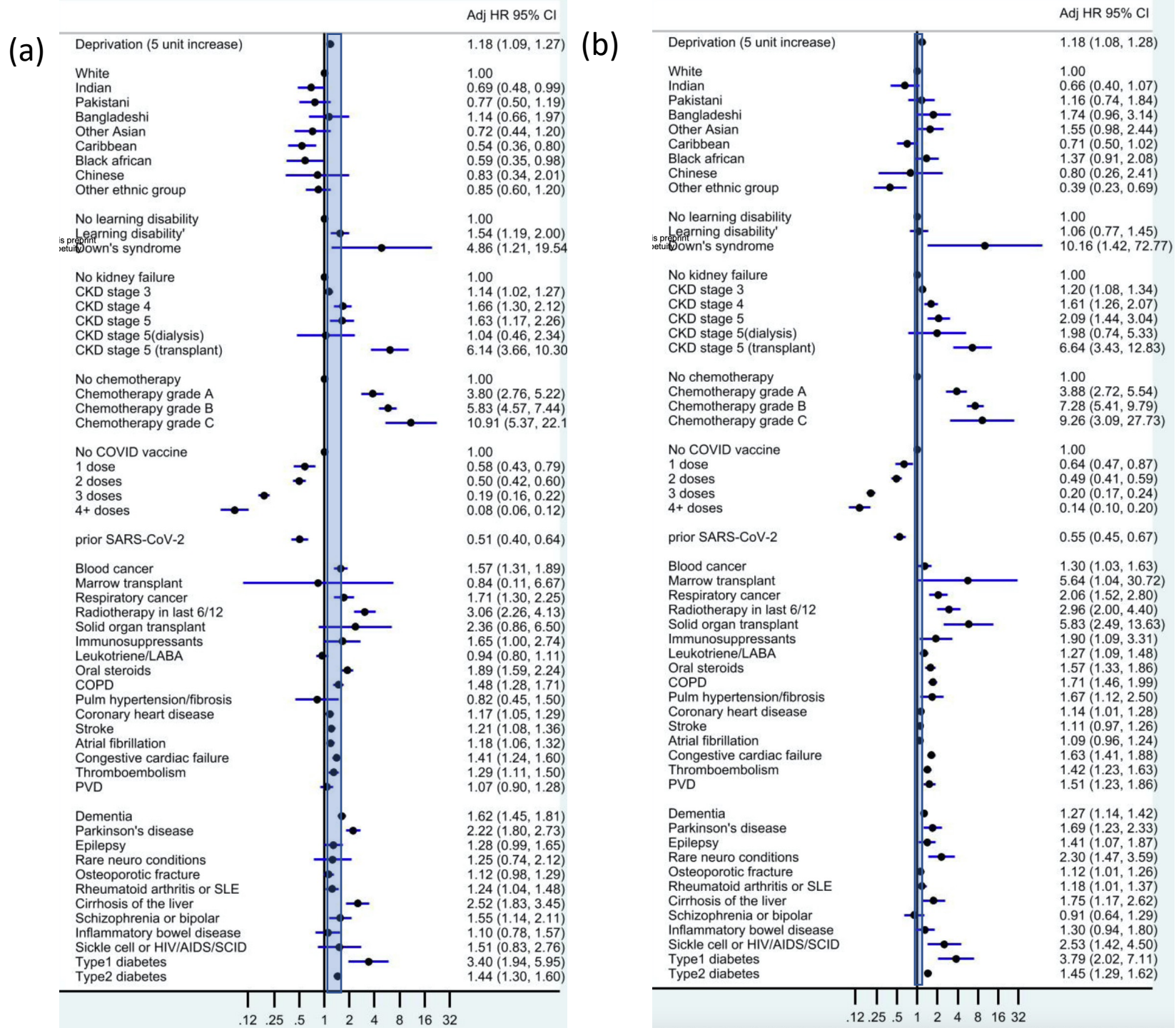
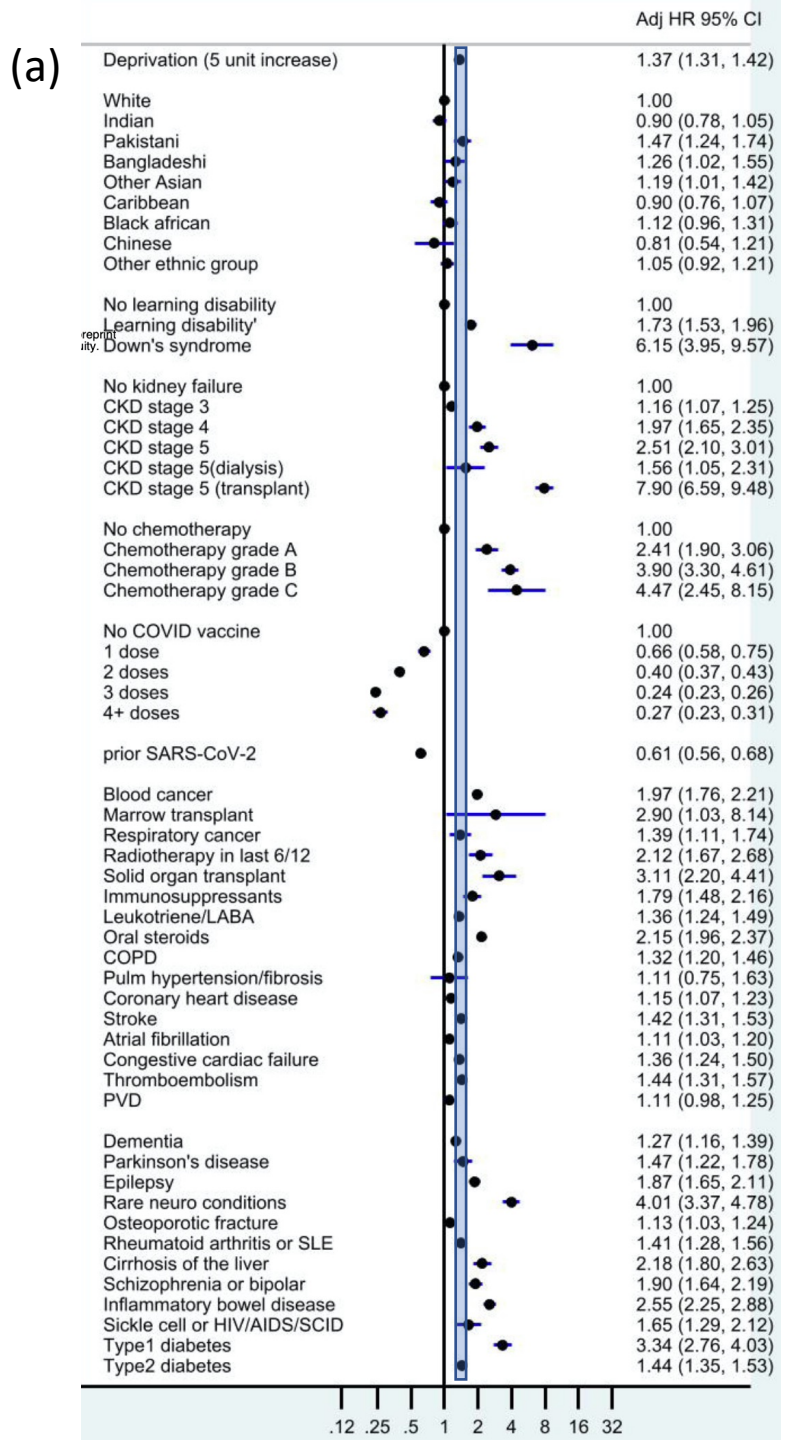


Figure 4 Adjusted hazard ratio of hospitalisation by clinical risk groups for males (a) and females (b). Adjustment for all variables including age and BMI. Adapted from [3].



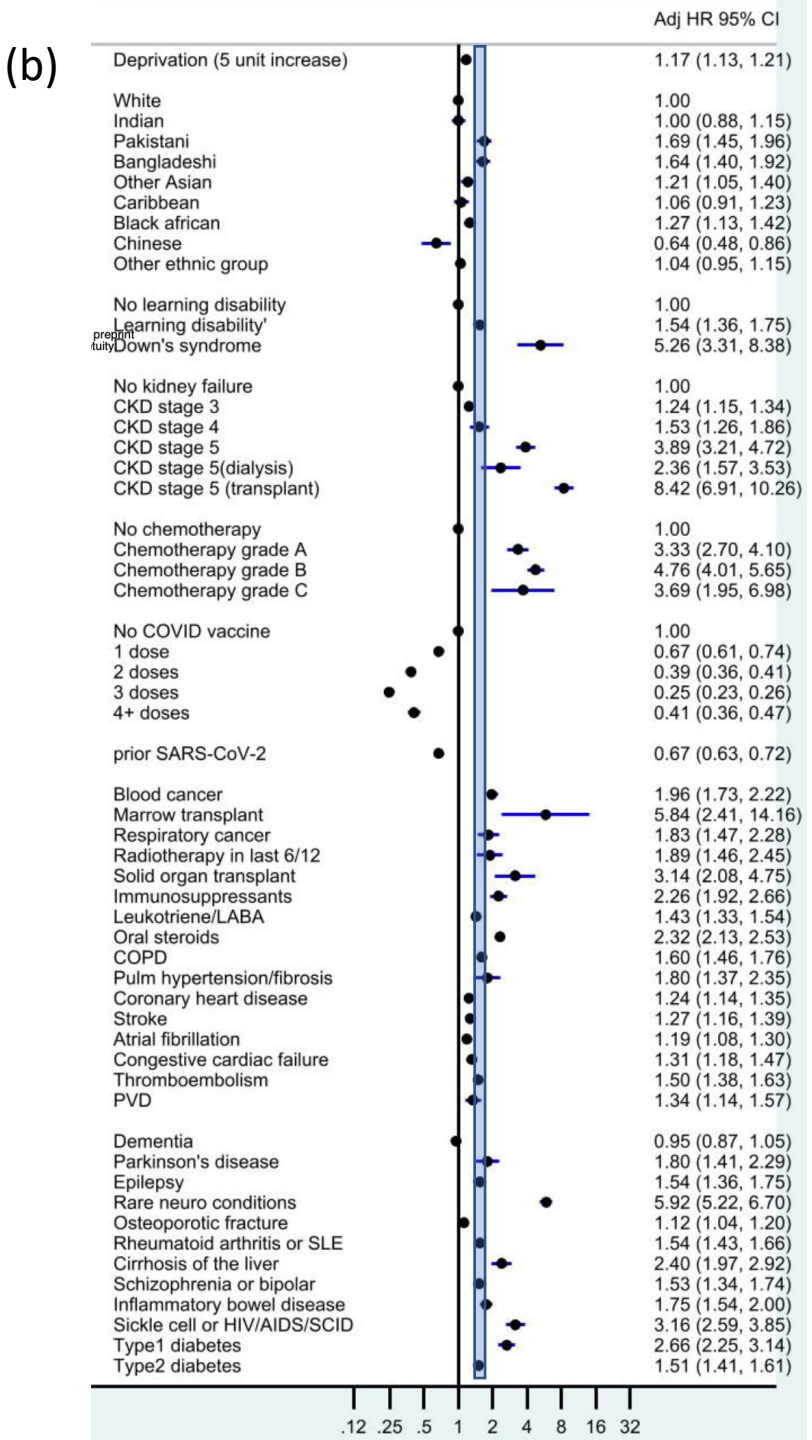


Figure 5. Sex- and age-standardised COVID-19-related death rates (IR) and 95% confidence intervals per 1,000 person-years in OpenSAFELY in the three pandemic waves. Models were standardised for age and sex using the European standard population except for the death rates by age group (not standardised) and death rates by sex (standardised by age). The 95% CI for the risk of COVID-19 death from rheumatoid arthritis, lupus and psoriasis in the third wave is highlighted with a blue shaded bar. Adapted from [1].

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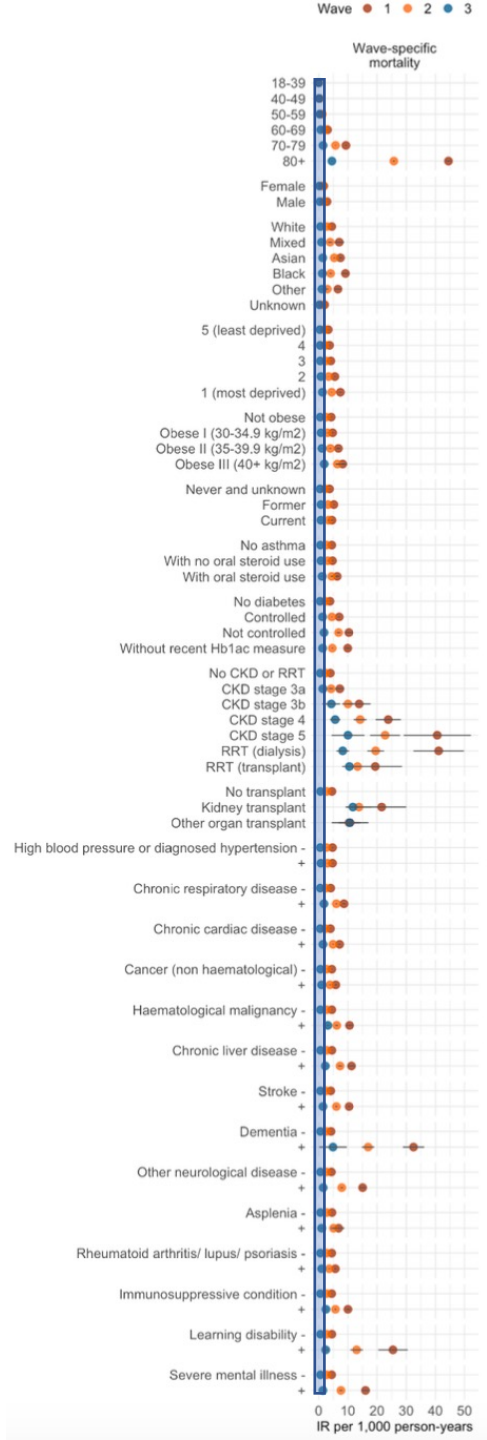

Therapeutics for people with COVID-19. An economic evaluation: EAG additional analysis post NICE Final Draft Guidance

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Abdullah Pandor, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Shijie Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
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Declared competing interests of the authors

Matt Stevenson provided advice to Astra Zeneca Rare Diseases regarding an unrelated intervention in an unrelated disease area. No other author declares a conflict of interest.

1 Introduction

This document should be read in conjunction with the initial EAG report[1], erratum[2], and EAG report following the NICE Appraisal Consultation Document[1], which provide more details on the work which has been undertaken.

In February 2023, NICE released its Final Draft Guidance (FDG) related to therapeutics for people with COVID-19.[3] In brief, the recommendations are (full details are provided in the FDG):

- Nirmatrelvir plus ritonavir (henceforth nirmatrelvir/ritonavir) is recommended for adults with COVID-19 provided they do not need supplemental oxygen and have an increased risk for progression to severe COVID-19 and defined in an independent advisory group report commissioned by the Department of Health and Social Care.[4] This report has been referred to by NICE as the 'McInnes report'.
- Sotrovimab is recommended for treating COVID-19 in people aged 12 years and over and weighing 40kg or more if they do not need supplemental oxygen and have an increased risk for progression to severe COVID-19 and defined in an independent advisory group report commissioned by the Department of Health and Social Care[4] and nirmatrelvir/ritonavir is contraindicated or unsuitable provided the company provides it according to an agreed commercial arrangement.
- Tocilizumab is recommended within its marketing authorisation for people with COVID-19 who are receiving systemic corticosteroids and that need supplemental oxygen or mechanical ventilation, provided the company provides it according to an agreed commercial arrangement.
- No other treatments (casirivimab and imdevimab, molnupiravir, remdesivir, and tixagevimab and cilgavimab) were recommended.

Following the second committee meeting, NICE was informed by the Department of Health and Social Care of the Therapeutics Clinical Review Panel modelling group's findings in the 'Edmunds report'. NICE was given pre-publication access to the Edmunds report which recommends inclusion of age ≥ 70 years within the high-risk group definition, since being 70 years or older may have similar risks of hospitalisation or death to other high-risk groups (such as rheumatoid arthritis, lupus or psoriasis) outlined in the McInnes report. NICE also requested from Pfizer additional data and analysis for this subgroup. In its response, Pfizer provided additional analyses using younger age groups. To inform a committee discussion on 4 April 2023, NICE explicitly instructed the EAG to exclude these and focus only on the analyses provided for the subgroup of patients without a high-risk condition that were 70 years or older, which were combined with patients at high-risk.

The EAG notes that had NICE not instructed the EAG to focus only on the subgroup of patients aged 70 years and older, that the results presented by Pfizer which included younger ages were not considered by the EAG to be appropriate for decision making. As an example, instead of analysing the age range of 65 to 69 years separately, these patients were subsumed into an age group of 65 years and older. The EAG has provided a stylised example of why the incremental cost-effectiveness ratios (ICERs) produced by this approach can be misleading. Table 1 shows incremental costs and incremental quality-adjusted life years (QALYs) scaled to the size of each group. In this example, three groups have markedly different ICERs, being £2000 for Group 1, £40,000 for Group 2 and £80,000 for Group 3. Assuming a cost per QALY gained threshold of £30,000 then neither Group 2 nor Group 3 would be considered cost-effective. However, Group 1 would be considered to be very cost-effective. When all three groups are combined the ICER remains low, and the combined group appears cost-effective because of the large influence of Group 1 which masks the fact that Group 2 and 3 are not cost-effective.

Table 1: Example illustrating potentially misleading ICERs due to combining groups

Group	Incremental Costs (£)	Incremental QALYs	ICER (£)
Group 1	1,000,000	500	2000
Group 2	200,000	5	40,000
Group 3	80,000	1	80,000
Combined groups	1,280,000	551	2,323

Section 2 details the analyses undertaken by the EAG. Section 3 details the results generated by these analyses. Results generated by the EAG are provided as ICERs, expressed in terms of cost per quality-adjusted life year (QALY) gained. Section 4 provides a comparison of the methodologies used by the EAG and Pfizer. Section 5 provides a comparison in the results generated by the EAG and by Pfizer.

2 The analyses run by EAG

The EAG used the same model structure as previously detailed but needed to update a number of parameters to represent a population aged 70 years and over.

The EAG ran two primary analyses based on the request from NICE. Both used the mean age of hospitalised ([redacted] years) and non-hospitalised patients ([redacted] years) for a cohort 70 years and over and the probability of hospitalisation ([redacted]) and death ([redacted]) associated with standard of care (SoC) in this cohort. These data were supplied as academic-in-confidence data from the PANORAMIC group. The two scenarios run by the EAG differed in the assumed efficacy of nirmatrelvir/ritonavir. In the first scenario the EAG has assumed that the efficacy for nirmatrelvir/ritonavir taken from Covid NMA[5] was applicable. In the second scenario, the EAG has assumed that the benefits taken from a Pfizer press release (June 2022) that provided EPIC-SR study results[6] were appropriate. This reported that 3/361 vaccinated adults with at least one risk factor for progression to severe COVID-19 were hospitalised or died in the nirmatrelvir/ritonavir arm compared with 7/360 vaccinated adults with at least one risk factor for progression to severe COVID-19 in the placebo arm. The EAG assumed that benefits reported in EPIC-SR were reduced hospitalisations only, as the EAG presumed that the company would have publicised any benefit in mortality, if any, and noted that earlier presented results had shown that all events had been hospitalisations with no deaths.[7]

The survival distributions for patients requiring supplemental oxygen and patients not requiring supplemental oxygen were calibrated so that the 28-day mortality rate for patients receiving SoC equalled [redacted]. No changes were made to data regarding time to discharge or change of patients' distributions between ordinal scales when in hospital as the EAG could not identify alternative data sources for this subgroup.

The parameter values that were used in the original high-risk population and in additional scenarios are summarised in Table 2.

Table 2: Parameter values used in the original high-risk population and in the scenarios modelling patients aged 70 years and over

	High-risk population (as in DFG)	70 years and over – Scenario 1	70 years and over – Scenario 2	High-risk population (as in DFG) plus 70 years and over - Scenario 3	The Pfizer analysis deemed by the EAG to be the most representative of NICE's request
Mean age of hospitalised patients (years)	55.0	[redacted]	[redacted]	70.0	[redacted]
Mean age of non-hospitalised patients (years)	55.0	[redacted]	[redacted]	65.0	[redacted]
Baseline hospitalisation rate (with SoC)	2.82%	[redacted]	[redacted]	2.82%	[redacted]
Baseline 28-day mortality rate (with SoC)	0.68%	[redacted]	[redacted]	0.68%	[redacted] / [redacted] [5]
Nirmatrelvir/ritonavir hospitalisation or death RR	Median: 0.13 95% CI: 0.07-0.27 Mean: 0.14[1]	Median: 0.13 95% CI: 0.07-0.27 Mean: 0.14[1]	Median: 0.43 95% CI: 0.11-1.64[3] Mean: 0.55[1]	Median: 0.13 95% CI: 0.07-0.27 Mean: 0.14[1]	[redacted]
Nirmatrelvir/ritonavir all-cause day 28 mortality RR	Median: 0.04 95% CI: 0.00[2]-0.63 Mean: 0.15[1]	Median: 0.04 95% CI: 0.00[2]-0.63 Mean: 0.15[1]	1[4]	Median: 0.04 95% CI: 0.00[2]-0.63 Mean: 0.15[1]	[redacted]

[1] Calculated by the EAG, [2] The EAG assumed a value of 0.001 in the high efficacy scenario, [3] The 95% upper CI was capped at 1 for the low efficacy scenario

[4] The EAG assumed no benefit in the absence of data on mortality only, [5] Depending if the model had been calibrated by Pfizer

The EAG highlights that the analyses run for people aged 70 years and over is different to other components of the high-risk population as individual ICERs have not been provided for conditions such as rheumatoid arthritis or lupus, with average values assumed applicable to all. Should the NICE appraisal committee wish to consider a similar approach for people aged 70 years and over, the EAG has undertaken an analysis (Scenario 3) where the previous high-risk population was run with only the age of patients increased. In this analysis, as the EAG does not have the data to allow a more informed estimated of the average age when all patients 70 years of age and over and other 'high-risk' patients are combined, patients who are hospitalised was set to an arbitrary value of 70 years, and the age of patients who are not hospitalised was set to an arbitrary value of 65 years. Academic-in-confidence data provided by Pfizer indicated that the addition of all patients over 70 years did not have a noticeable impact on the average age increasing it to [redacted] years from 55 years. This appeared potentially incorrect to the EAG as the average age of hospitalised patients over the age of 70 years was [redacted] years and the average age of non-hospitalised patients over the age of 70 years was [redacted] years and the average for other high-risk patients was 55 years. However, if these data were correct then the original EAG analyses would provide a reasonable estimate of the cost-effectiveness of nirmatrelvir/ritonavir if an average ICER was desired.

3 The results generated by the EAG

Mean efficacy results

The results of the mean efficacy analysis for patients at high-risk of hospitalisation are shown in Table 3. The results from the three scenarios produce markedly different ICERs, ranging from below £6000 per QALY gained to above £60,000 per QALY gained.

Table 3: Mean efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC[†](£)	NMB compared with SoC[††] (£)
Scenario 1 (baseline rates from PANORAMIC + efficacy data from COVID-NMA)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1761	6.55	26,381	-254	144
Scenario 2 (baseline rates from PANORAMIC + efficacy data from EPIC-SR with assumptions)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1811	6.53	61,454	-742	-563
Scenario 3 (baseline rates from previous high-risk analyses, efficacy data from COVID-NMA and starting ages of 70 and 65 for hospitalised and non-hospitalised patients)					
SoC	1053	9.97	-	-	-
Nirmatrelvir/ritonavir	1805	10.10	5516	1975	3339

[†] Assuming a threshold of £20,000 per QALY gained [††] Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care

High efficacy results

The results of the high efficacy analysis for patients at high-risk of hospitalisation are shown in Table 4. The results from the three scenarios produce noticeably different ICERs, although all ICERs remain below £30,000 per QALY gained.

Table 4: High efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC[†](£)	NMB compared with SoC[††] (£)
Scenario 1 (baseline rates from PANORAMIC + efficacy data from COVID-NMA)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1763	6.55	24,147	-181	255
Scenario 2 (baseline rates from PANORAMIC + efficacy data from EPIC-SR with assumptions)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1736	6.55	26,245	-244	147
Scenario 3 (baseline rates from previous high-risk analyses, efficacy data from COVID-NMA and starting ages of 70 and 65 for hospitalised and non-hospitalised patients)					
SoC	1053	9.97	-	-	-
Nirmatrelvir/ritonavir	1817	10.12	5024	2277	3797

[†] Assuming a threshold of £20,000 per QALY gained [††] Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care

Low efficacy results

The results of the low efficacy analysis for patients at high-risk of hospitalisation are shown in Table 5. The results from the three scenarios produce markedly different ICERs, ranging from below £8000 per QALY gained to being dominated, as the there were no assumed QALY gained in Scenario 2 when low efficacy is assumed.

Table 5: Low efficacy results for people at high-risk of hospitalisation

Intervention	Discounted Costs (£)	Discounted QALYs	Cost per QALY compared with SoC (£)	NMB compared with SoC[†](£)	NMB compared with SoC[††] (£)
Scenario 1 (baseline rates from PANORAMIC + efficacy data from COVID-NMA)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1766	6.54	33,615	-427	-113
Scenario 2 (baseline rates from PANORAMIC + efficacy data from EPIC-SR with assumptions)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1950	6.51	Dominated	-1239	-1239
Scenario 3 (baseline rates from previous high-risk analyses, efficacy data from COVID-NMA and starting ages of 70 and 65 for hospitalised and non-hospitalised patients)					
SoC	1053	9.97	-	-	-
Nirmatrelvir/ritonavir	1817	10.07	7827	1188	2164

[†] Assuming a threshold of £20,000 per QALY gained [††] Assuming a threshold of £30,000 per QALY gained
QALY – quality-adjusted life years; SoC – standard of care

Sensitivity Analysis Results

The EAG ran three sets of the sensitivity analyses: amending the duration for long COVID (by doubling and halving); assuming baseline hospitalisation rates of 5%; and changing the SMR values associated with long COVID (to 5 and 10). The results from the sensitivity analyses are presented as net monetary benefits (NMBs). For ease of comparison, the base case NMBs are presented in Figure 1 for a willingness-to-pay (WTP) of £20,000 per QALY and Figure 2 for a WTP of £30,000 per QALY.

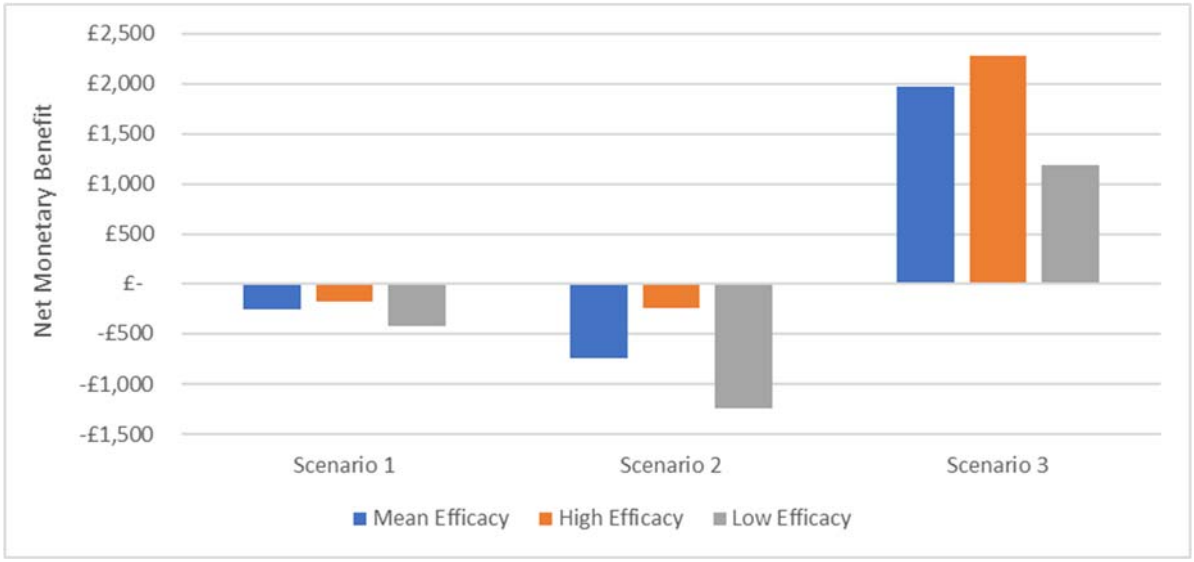

Figure 1: Base case NMBs assuming a WTP of £20,000 per QALY

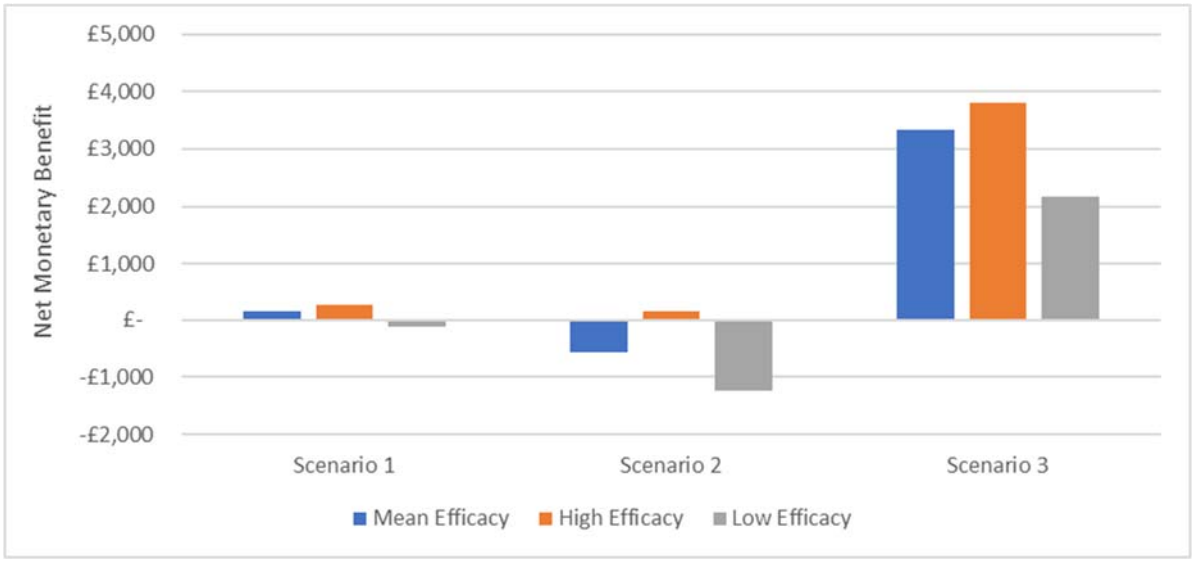

Figure 2: Base case NMBs assuming a WTP of £30,000 per QALY

Amending the duration of long COVID

Figure 3 and Figure 4 present the NMBs for WTP of £20,000 and £30,000, respectively when the duration of long COVID is halved. There are two changes in sign of NMBs when a willingness to pay of £30,000 is used. These were for Scenario 1 and Scenario 2 when mean efficacy estimates are used. In these scenarios the NMB becomes negative where they were originally positive.

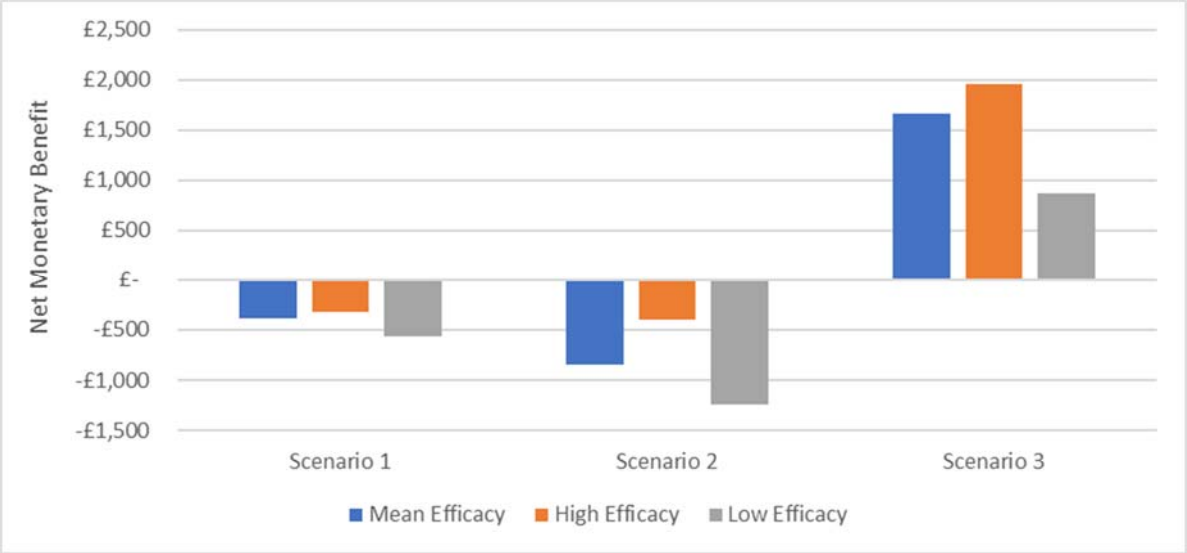

Figure 3: NMBs when long COVID duration is halved assuming a WTP of £20,000 per QALY

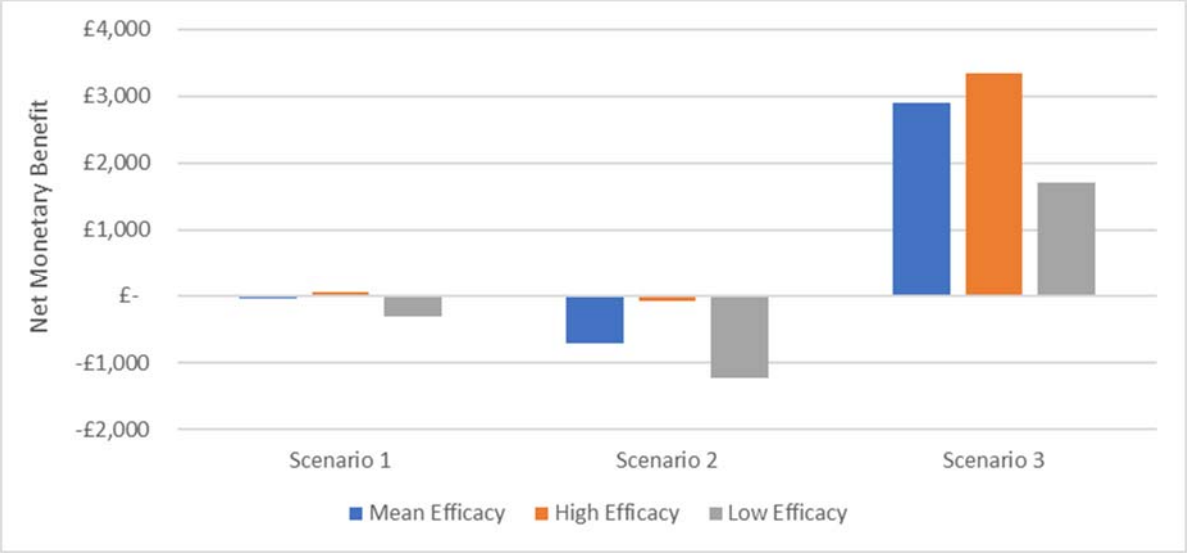

Figure 4: NMBs when long COVID duration is halved assuming a WTP of £30,000 per QALY

Figure 5 and Figure 6 present the NMBs for WTP of £20,000 and £30,000, respectively when the duration of long COVID is doubled. There were no changes in the sign of the NMB in any scenario.

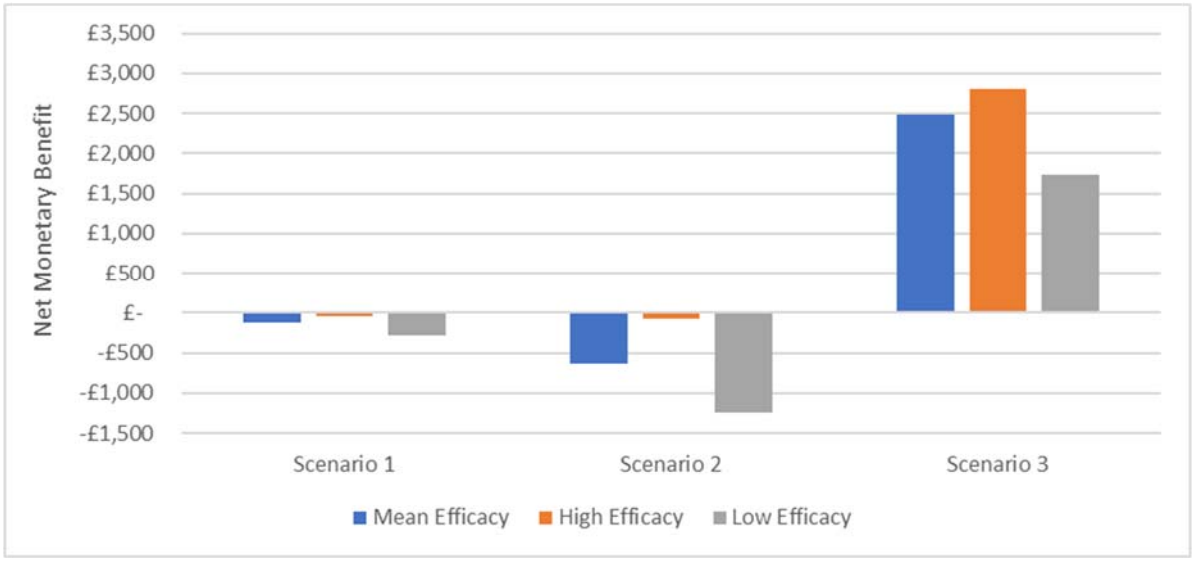

Figure 5: NMBs when long COVID duration is doubled assuming a WTP of £20,000 per QALY

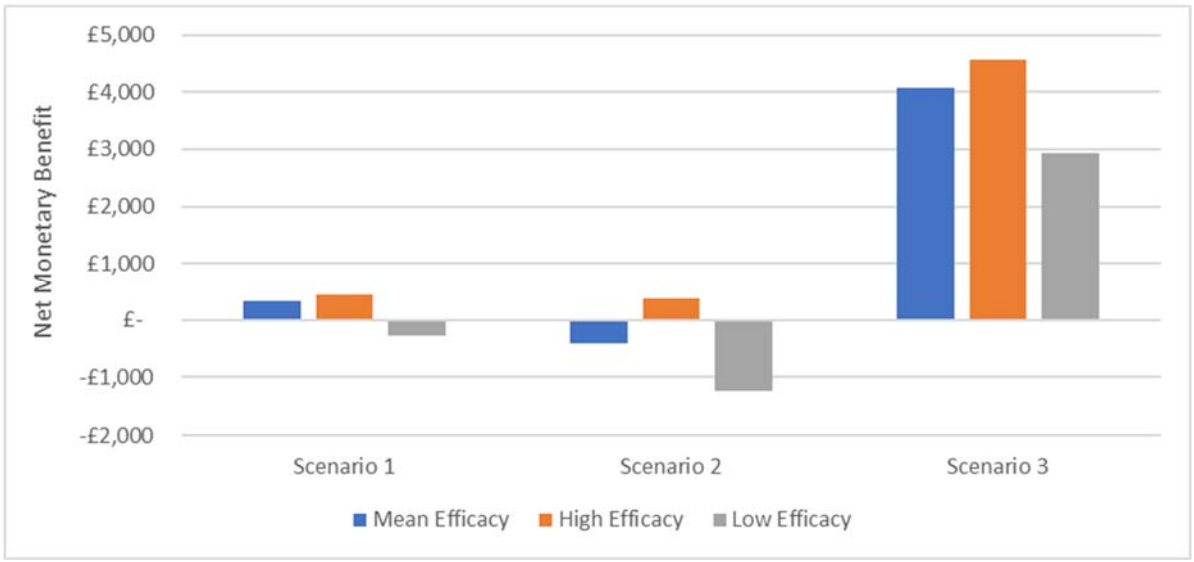

Figure 6: NMBs when long COVID duration is doubled assuming a WTP of £30,000 per QALY

Amending the hospital admission percentage

Figure 7 and Figure 8 present the NMBs for WTP of £20,000 and £30,000, respectively when a hospital admission rate of 5% is assumed. All ICERs are below £20,000 except for Scenario 2 where low efficacy estimates are assumed, as nirmatrelvir/ritonavir is not modelled to give any increase in QALYs and is thus dominated by SoC. Further increases in the hospitalisation rate would make the ICERs more favourable to nirmatrelvir/ritonavir, with the exception of Scenario 2 with low efficacy.

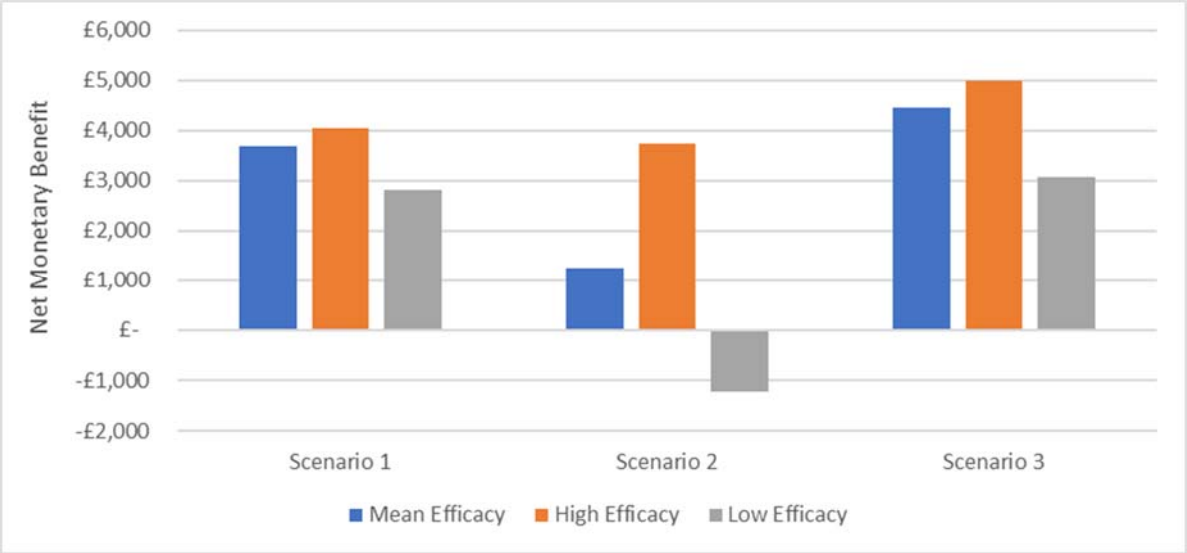

Figure 7: NMBs with a hospitalisation rate of 5% assuming a WTP of £20,000 per QALY

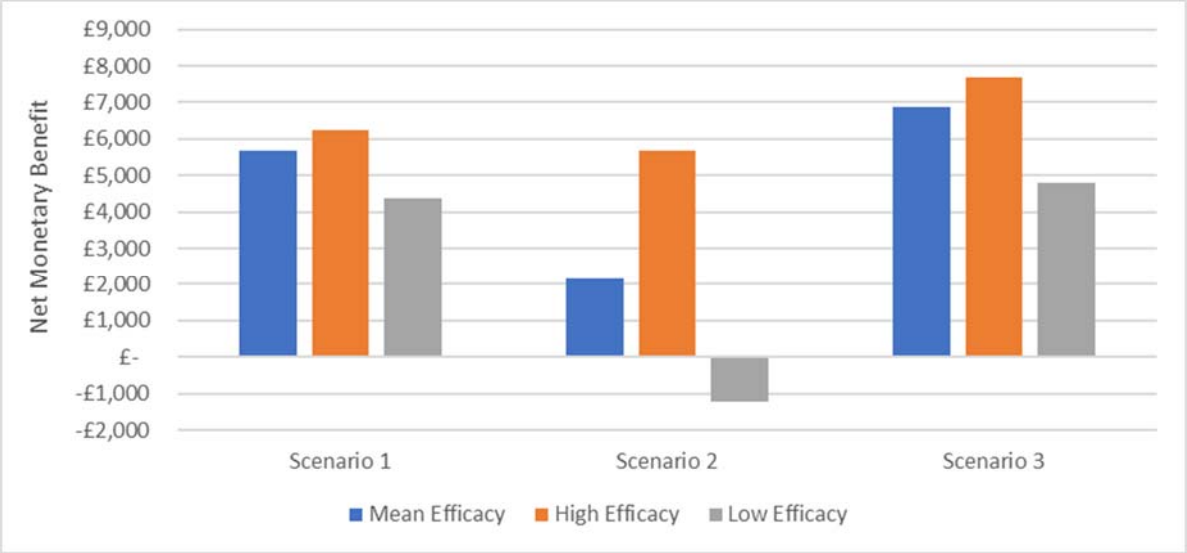

Figure 8: NMBs with a hospitalisation rate of 5% assuming a WTP of £30,000 per QALY

Changing the SMR for people with long COVID

Figure 9 and Figure 10 present the NMBs for WTP of £20,000 and £30,000, respectively when an SMR value of 5 is assumed for patients with long COVID. There were no changes observed in the sign of the NMB in any scenario.

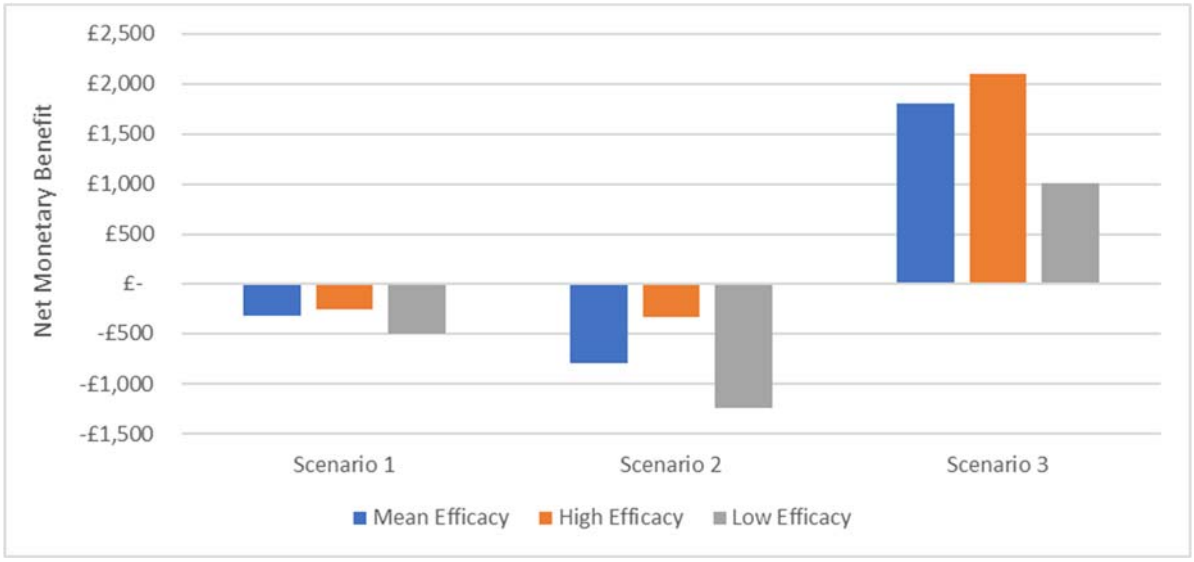

Figure 9: NMBs with an SMR value of 5 assuming a WTP of £20,000 per QALY

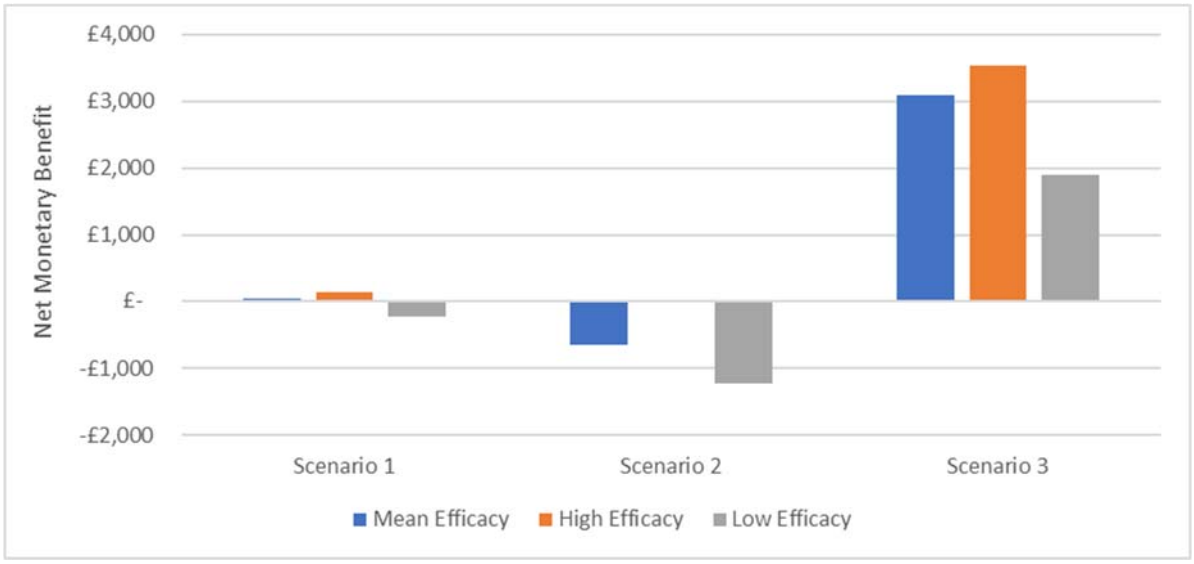

Figure 10: NMBs with an SMR value of 5 assuming a WTP of £30,000 per QALY

Figure 11 and Figure 12 present the NMBs for WTP of £20,000 and £30,000, respectively when an SMR value of 10 is assumed for patients with long COVID. There were no changes observed in the sign of the NMB in any scenario.

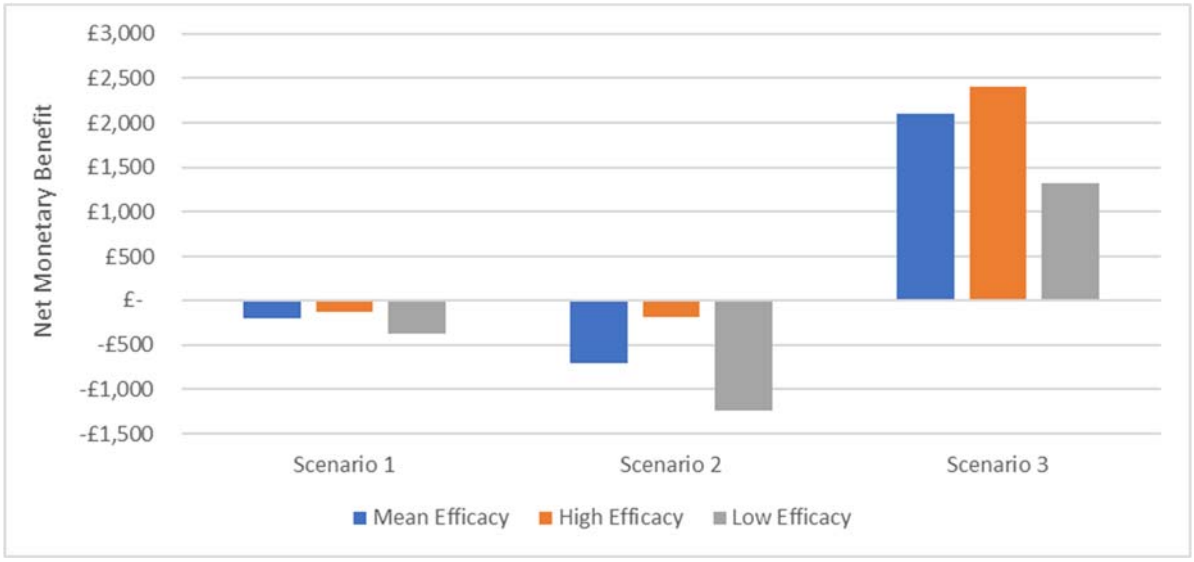

Figure 11: NMBs with an SMR value of 10 assuming a WTP of £20,000 per QALY

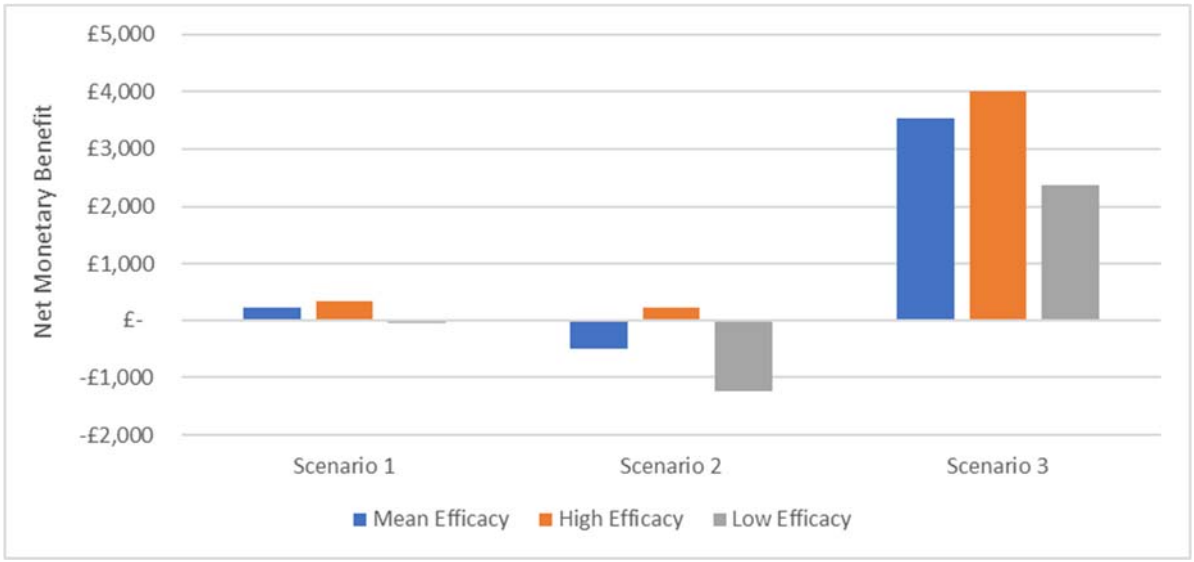

Figure 12: NMBs with an SMR value of 10 assuming a WTP of £30,000 per QALY

4 Comparison of the methodology used by the EAG and that used by Pfizer

This section compares the methodology used by the EAG and Pfizer. These are discussed in Section 4.1 to Section 4.4. The EAG has focussed only on the results provided by Pfizer for the 'All 70+ and 18–69 years old with at least one pre-existing health condition' subgroup.

4.1 The population and hospitalisation probability

The EAG has analysed a population of people who are aged 70 years and over. The company has included this group within a combined population of '*All aged 70+ with at least one pre-existing health condition*'. This results in slightly different hospitalisation probabilities between the two analyses being [redacted] in the EAG's analysis and [redacted] in the Pfizer's analysis. These values may indicate that the value of 2.82% hospitalisation rate for high-risk patients from Patel *et al*.[8] used in previous analyses appears high, however, as highlighted by Pfizer the data from PANORAMIC "*underestimates baseline hospitalisation and mortality rates of the full population at risk of severe COVID-19 disease as it excludes the highest risk population who can already access treatment though COVID medicine delivery units*". Both the results generated by Pfizer and the EAG may therefore be unfavourable to nirmatrelvir/ritonavir.

The age of the cohort also differs between the EAG and Pfizer. The EAG uses values for a population aged 70 years and over: hospitalised patients ([redacted] years) and non-hospitalised patients ([redacted] years) whereas Pfizer uses a considerably lower value ([redacted] years). As Pfizer have assumed a lower age than the EAG, its analyses will provide more QALYs per death avoided then the analyses undertaken by the EAG and will be slightly more favourable to nirmatrelvir/ritonavir.

4.2 The assumed efficacy of nirmatrelvir/ritonavir in reducing hospitalisations and death

In its original analyses, the EAG used the efficacy reported by Covid-NMA to estimate the benefits associated with nirmatrelvir/ritonavir treatment. These were 0.13 (95% CI 0.07 – 0.27) for hospitalisation or death and 0.04 (95% CI 0.00 – 0.63) for death, with the EAG using the mean from these distributions in its mean efficacy analyses: 0.14 for hospitalisation or death, and 0.15 for death. These values have been maintained in Scenario 1. However, for Scenario 2, the treatment efficacy has been estimated from a Pfizer press release concerning EPIC-SR, resulting in a distribution for the relative risk of hospitalisation or death of 0.43 (95% CI 0.11 – 1.64) [Mean 0.55] and an assumption that there was no impact on mortality.

Contrastingly, Pfizer has used different data which assumes that nirmatrelvir/ritonavir treatment has a relative risk of [redacted] for hospitalisation or death, and also for death. [redacted] Pfizer states

that it identified a factual inaccuracy in the population on the EAG's model, as there were no deaths in the nirmatrelvir/ritonavir arm of EPIC-HR and that therefore the distribution of 0.04 (95% CI 0.00 – 0.63) used for death is incorrect. The EAG notes that these data are provided by COVID-NMA, and comments that the distribution will utilise a continuity correction to adjust for small numbers of observed events. Where there are a small number of observations it can appear that the transition probabilities are more certain than they truly are, and it is common for continuity corrections to be performed to reduce this limitation. The EAG therefore disagrees with the values chosen by Pfizer to estimate the effectiveness of nirmatrelvir/ritonavir and notes that this will favour nirmatrelvir/ritonavir

4.3 The probability of mortality due to COVID-19 in the model for patients on SoC

As shown in Table 2, the EAG has used a value for the probability of mortality due to COVID-19 ([redacted]) that is higher than the value intended to be used by Pfizer ([redacted]). The EAG analysis is therefore more favourable to nirmatrelvir/ritonavir when it has a beneficial impact of mortality if Pfizer has implemented its value correctly. In order to change the mortality probability, the model needs to be calibrated. The EAG does not know if Pfizer did recalibrate the model; if Pfizer had not recalibrated the model, a probability of death higher than in the EAG analyses would have been used ([redacted]).

4.4 Using SOLVER to ensure that the correct number of deaths are simulated

As the relative risks of hospitalisation or death and the relative risk of death are correlated care must be taken to ensure that the number of deaths are as intended, with the EAG having assumed for simplicity that all deaths occur in hospital. Maintaining logical consistency is achieved using the SOLVER add-in within Excel. It is unclear whether Pfizer has run SOLVER before generating results; if it has not, then the results will not be representative of the intended analyses.

5 Comparison of the results generated by the EAG and those generated by Pfizer

The results generated by the EAG are heavily dependent on the scenario chosen, which importantly differ in terms of the assumed hospitalisation probability and the mortality probability. The scenarios produce ICERs that are lower than £6000 per QALY gained or that indicative that nirmatrelvir/ritonavir is dominated.

The results produced by Pfizer in the scenario selected in Table 2 (which are reported in Table 2 of Pfizer's response) suggested an ICER of approximately £22,000, although there appears to be typographical errors as the value was equal in all of the high, mean and low efficacy scenarios. Given the differences in the methodologies highlighted in Section 4 it is not surprising that there are differences in the results generated by the EAG and those generated by Pfizer. However, the ICER from Scenario 1 high efficacy (£24,147) is moderately above that reported by the company (£21,524) which the EAG believes is intuitive given the relative similarity in parameter inputs if the model was not calibrated, although there would still be uncertainty in Pfizer's estimate if SOLVER had not been run.

6 References

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