Review of the evidence for Scottish Government advice to people on Scotland's Highest Risk List

April 2022

Scottish Government
Riaghaltas na h-Alba
gov.scot

Foreword

At the beginning of the COVID-19 pandemic in March 2020, the four Chief Medical Officers across the UK agreed a range of treatments and health conditions[1] which they believed, based on the limited evidence available at that point, would mean that people might be at higher risk of severe illness or death if they caught the virus. These people were asked to shield for a period of 18 weeks, until the end of July 2020.

This report reviews the evidence that has emerged during the past two years, with particular focus on the vaccination programme and how this is working to protect the majority of the 177,000 people on the Highest Risk List (HRL), formally known as the Shielding List.

Throughout the COVID-19 pandemic, I and a team of 30 medical specialists have reviewed new research, data and insight from clinicians and scientists as it has emerged. This evidence has underpinned the advice we have provided to people on the Highest Risk List.

There has, rightly, been much interest in the Scottish Government's strategy of shielding, which had a major and lasting impact on people's lives. We asked all those at highest risk to strictly self-isolate for 12 weeks. We know how hard that was, and we know how frightening this past two years has been for many people.

Our strategy at the beginning was entirely focused on saving lives and protecting people at highest risk. There was very little data about COVID-19 risk factors at that point. Shielding was introduced as one of the few interventions available to us.

I have high confidence that the approach we took did protect people from catching COVID-19. Whilst it's difficult to quantify, as we don't know what would have happened had we not asked people to shield, it is a reasonable and logical conclusion that shielding saved lives.

However, we also know that asking people to isolate away from friends, family and society in general had a negative and lasting impact on people psychologically and socially. The rollout of the vaccine programme has changed the context significantly. The evidence on the effectiveness of vaccines for people on the Highest Risk List, coupled with the availability and efficacy of new treatments such as antivirals, immune modulators and monoclonal antibodies, has allowed us to take a different approach.

There is now, two years on, a far better understanding of the range of risk factors that may put someone at increased risk of becoming seriously unwell from COVID-19. This report sets out the strong base of evidence which shows that the COVID-19 vaccine is offering significant protection and preventing people on the Highest Risk List from becoming severely ill. Furthermore, death rates as a result of COVID-19 amongst people on the Highest Risk List have significantly reduced and there is now

[1] COVID Highest Risk - Highest Risk Classifiaction - Scottish Government - Publications (www.gov.scot)

a far better understanding of the impact of COVID-19 on those with specific clinical conditions.

Whilst there are people who do have a higher risk from COVID-19 even following vaccination – primarily people whose immune systems are suppressed or compromised due to a health condition or treatment - the evidence set out in this paper clearly points to the reduced clinical risk for the majority of people on the Highest Risk List. This clear evidence underpins our decision to end the Highest Risk List at the end of May 2022 in Scotland.

Scotland's Chief Medical Officer will write to everyone on the Highest Risk List in the coming weeks to explain this decision, and to set out the identification process the NHS will retain to be able to quickly identify people who should be prioritised for vaccination, treatments and, if the threat level increases, for additional protective advice. In the meantime, we are asking people who have been on the Highest Risk List to follow the same advice in relation to COVID-19 as the rest of the population, unless advised otherwise by their GP and clinician, who know them and their specific health condition best.

Dr John Harden
Deputy National Clinical Director, Clinical Advisor for the Highest Risk List
Scottish Government

Introduction

This Evidence Review sets out the data from clinical and scientific studies from Scotland, UK and internationally which show how the vaccination programme has made a significant difference to people on the Highest Risk List, including to many who are immunosuppressed or immunocompromised.

The report sets out the expert views of medical specialists who have advised the Scottish Government throughout the pandemic.

The report also presents analysis based on Public Health Scotland figures on COVID-19 related deaths amongst people on Scotland's Highest Risk List.

The Review is designed for two audiences: firstly, people on the Highest Risk List themselves, and secondly, GPs, clinicians and third sector organisations which support people with the range of conditions which have put them on the Highest Risk List. This latter audience will be able to use the Review to assist discussions about risk with individual patients and the people they support. Annex D provides a high level summary of findings from this Review for each Highest Risk Group which can assist GPs and Clinicians in discussions with patients.

While the evidence set out in this Evidence Review is published and readily available, it is not always easy to understand or to translate the wide body of often very technical data and scientific evidence to inform choice. More detailed information and analysis is found in the Annexes to this report.

Executive Summary

A systematic review of each of the original groupings of people on the Highest Risk List pinpoints the groups which clinicians advise now have a significantly reduced risk, and the groups which still have a higher level of risk. We will publish separate guidance for these two groups.

The groups of people who do still have a higher risk are as follows:

- Group 1 – Transplant
- Group 2 – Cancer
- Group 5 - Immunosuppression

This review supports the conclusion that there is no longer a purpose for, or need to retain the Highest Risk List.

Contents

Background to Scotland's Shielding List

1.1 The Scottish Government's Shielding strategy was designed to protect those who may be at significantly increased risk of serious illness or death from COVID-19 by supporting them to stay at home and limit their exposure to the virus.

1.2 With little data available about COVID-19 risk factors at the outset of the pandemic, the UK Chief Medical Officers agreed a list of conditions and treatments considered to increase risk, based on our understanding of individuals' vulnerability to other known respiratory viruses.

1.3 The Shielding List was created in March 2020. Around 180,000 people in Scotland, considered to be at highest clinical risk from COVID-19, received a letter from the Scottish Chief Medical Officer, advising them to strictly self-isolate (shield) for a 12- week period. The Shielding period was extended further with some relaxations of the initial strict self-isolating shielding guidance until 31 July 2020 when Shielding was paused.

1.4 By this stage, the evidence, primarily from an evaluation of the Shielding Programme conducted by Public Health Scotland[2], pointed clearly to the significant and detrimental impact of shielding on people's physical and mental health and wellbeing. Our aim moved to provide information, advice and tools to enable and empower those at highest risk to make informed decisions about their day to day activities and interactions; and, to consider what level of protection was right for them, as well as to support physical and mental health and wellbeing more generally.

1.5 User research has been undertaken with people on the Highest Risk throughout the course of the pandemic to better understand the impacts on their lives. The first findings from a survey by Public Health Scotland of the shielding group were published in September 2020. This showed that people who were advised to shield had mostly followed the advice, but that the shielding experience was difficult, in particular for socio-economically vulnerable groups[3]. The first full findings from the evaluation, which covered the period between March and August 2020, were published in January 2021. This found clear evidence that the shielding advice changed people's behaviour and that the shielding support addressed real need.

1.6 Public Health Scotland was then asked by the Scottish Government to evaluate the guidance and support offered to the highest risk group following the pause in shielding. A second survey was run and the findings from this were published in March 2022. This findings highlight ongoing negative impacts on the lives of people in the highest risk group, but also show that the advice and support offered to the highest risk group made a difference[4].

---

[2] COVID-19 Shielding Programme (Scotland) rapid evaluation - full report (publichealthscotland.scot)
[3] COVID-19 Shielding Programme (Scotland) Impact and Experience Survey - Repository - Public Health Scotland
[4] COVID-19 shielding programme (Scotland) impact and experience survey – part two 30 March 2022 - COVID-19 shielding programme (Scotland) impact and experience survey – part two - Publications - Public Health Scotland

2. Highest Risk List Criteria

2.1 The conditions and treatments included in the initial shielding list were:

• Solid organ transplant recipients who remain on long-term immune suppression therapy.
• People with specific cancers.
• People with severe respiratory conditions including all people with cystic fibrosis, severe asthma and severe chronic obstructive pulmonary disease (COPD).
• People with rare diseases and inborn errors of metabolism that significantly increase the risk of infections (such as severe combined immunodeficiency and homozygous sickle cell).
• People on immunosuppression therapies sufficient to significantly increase risk of infection.
• People who are pregnant with significant heart disease.

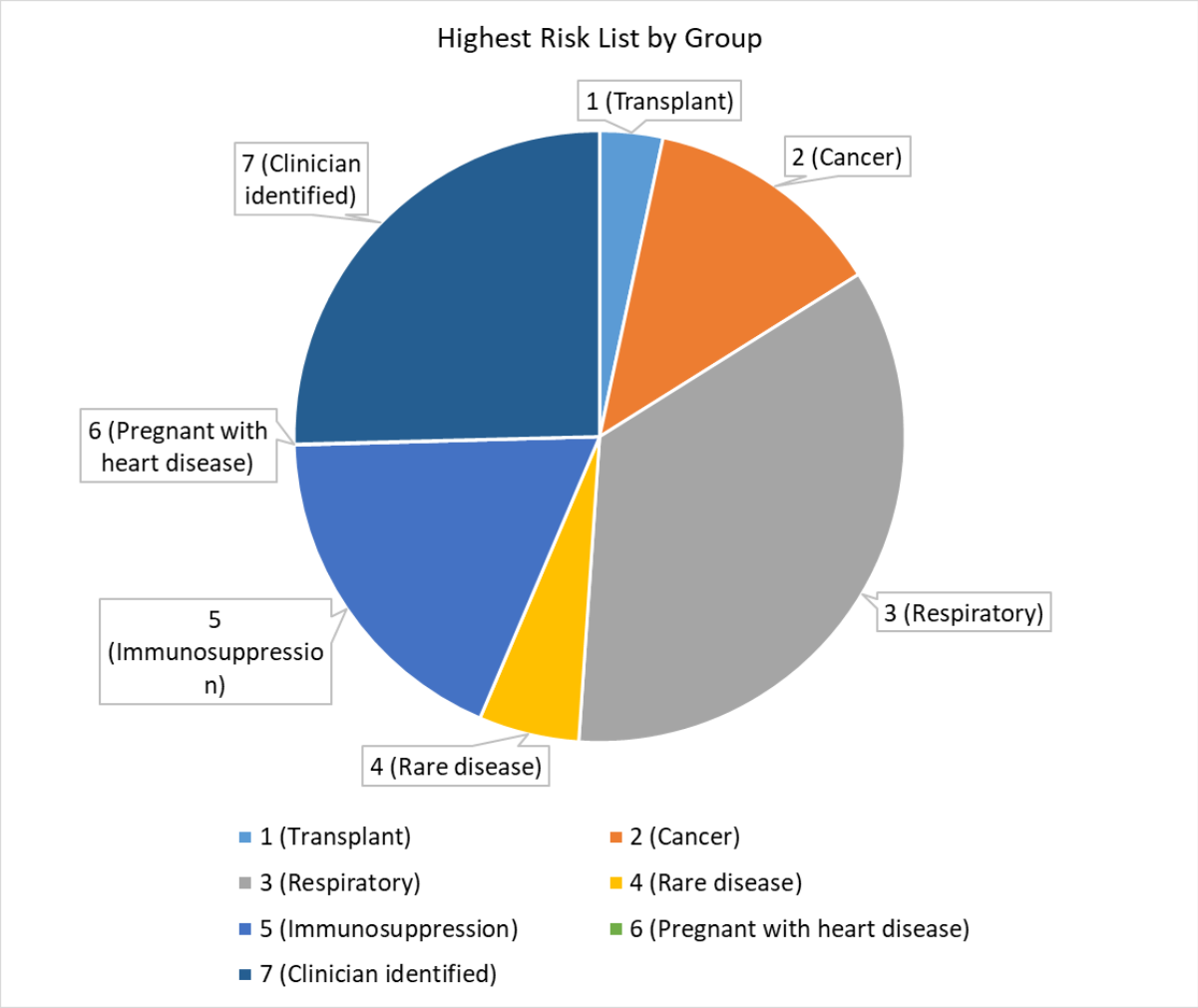
2.2 As evidence of COVID-19 continued to emerge, a better understanding of the wider range of risk factors putting individuals at increased risk of becoming seriously ill from COVID-19 has developed and the following conditions were added:
• People on home oxygen
• People with severe bronchiectasis and pulmonary hypertension
• People who have had their spleen removed
• People on renal dialysis
• People with Down Syndrome
• People with chronic kidney disease

2.3 Clinicians were able to add people who did not fall into any of the six pre-defined groups, based on their clinical judgement.

2.4 As at 21 February 2022, 177,475 people in Scotland were identified as being at highest risk to COVID-19 and were on the Highest Risk List[5]. This makes up around 3% of the general population.

[5] COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

Figure 1 – Shows the seven groups which make up the Highest Risk List. *The same individual may be counted in more than one group.



3. Timeline of advice

3.1 Scotland moved beyond Level 0 in August 2021 where precautionary measures remained in place for the general population. This advice and baseline measures continued from August 2021 to March 2022. The publication of the update to Scotland's Strategic Framework[6] in 2022 made clear that due to the progress in vaccination and treatments, the intention was to rely much less on legal requirements going forwards and much more on people and organisations taking basic, sensible steps to reduce the risk of and harm from COVID-19.

[6] Supporting documents - Coronavirus (COVID-19): Scotland's Strategic Framework update - February 2022 - gov.scot (www.gov.scot)

Figure 2 - Timeline of Advice for Highest Risk List.

Date	Summary of Advice for Highest Risk List
Mar 2020	HRL created (circa. 180,000 people). Advice to shield for 12 week period.
Jun 2020	Shielding extended for a further 4 week period.
Aug 2020	Shielding paused. HRL to follow general population advice.
Oct 2020	Introduced Protection Levels and Extra Advice. HRL advised not to attend work/school/college in Level 4 or above.
Apr 2021	Scotland move to Level 3. HRL advised safe to return to work/school/college.
Jul 2021	Scotland move to Level 0. HRL to follow general population advice, unless advised otherwise by their GP or clinician.
Aug 2021	Scotland moved beyond Level 0. Protection measures for general public remained in place.
Nov 2021	Update to Strategic Framework. Protective measures for general public remain in place.
Feb 2022	Update to Strategic Framework. Health measures and adaptations to be Scotland's primary means of managing COVID-19.
Mar 2022	Scotland removed some protective measures. Legal requirements to wear face coverings in public places remained in place.
Apr 2022	Scotland removed final legal measures.
May 2022	Retiring of HRL. Identification process to be stood up. Guidance for people who are severely immuno-suppressed to be published.

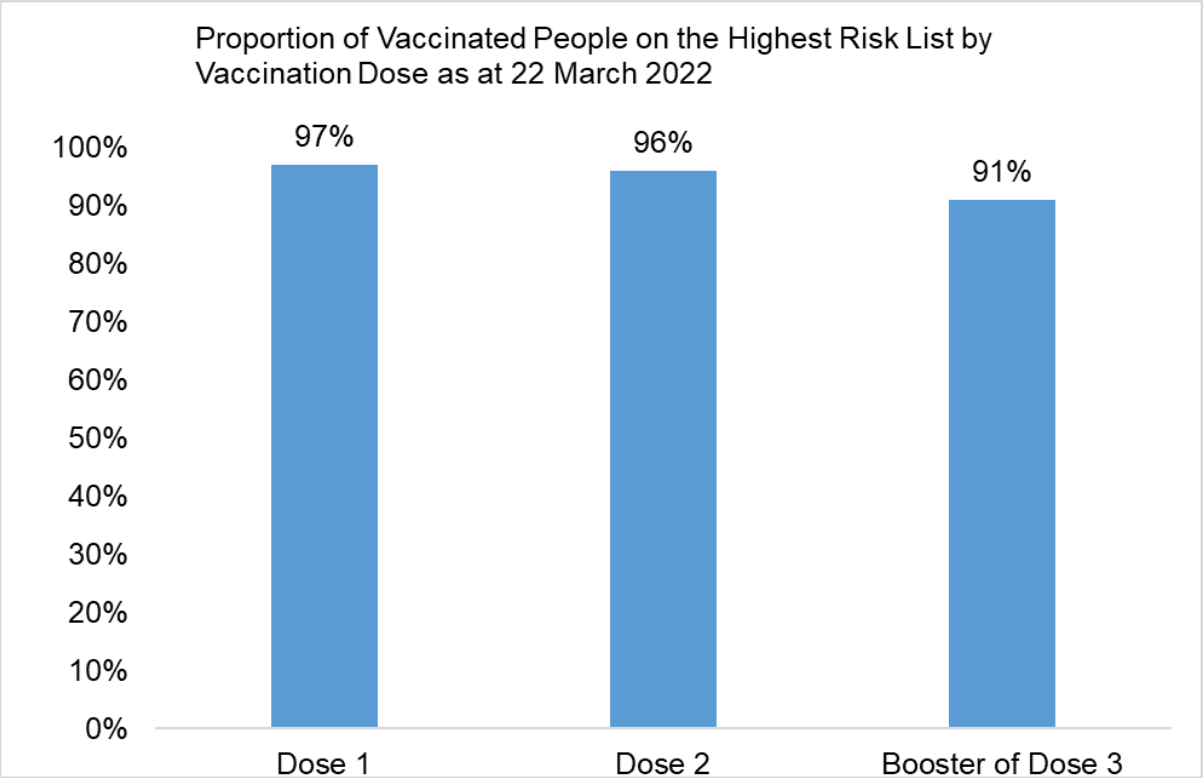
Vaccine efficacy and effectiveness for people on the Highest Risk List

4. Vaccination rates[7]

4.1 Vaccination has progressed extremely well for the Highest Risk List population with approximately 96% of highest risk individuals now having received two doses, and around 91% having received a third dose or booster, as shown in figure 3 below.

[7] COVID-19 Daily Dashboard | Tableau Public

Figure 1 - Vaccination rates of people on the Highest Risk List at each primary dose stage.



4.2 In addition, 89% of everyone over 18 years of age in Scotland have now received their second dose, and over 77% have received a third dose or booster.

4.3 We know that vaccinated individuals can still transmit the virus but we also know that vaccinated individuals are less likely to become infected or to become seriously ill and require hospitalisation.

4.4 People who are aged 12 and over with a weakened immune system, people aged over 75 and people in care homes are being offered a second booster dose in Spring 2022[8].

5. Vaccine efficacy and effectiveness studies

5.1 Annex A details a review of relevant studies on vaccine efficacy and effectiveness that have informed Scottish Government COVID-19 Highest Risk policy. It includes summaries of the main findings and their key limitations.

5.2 This is not a complete list of studies on vaccine efficacy for the Highest Risk List. Readers should note that studies included in this list measure different things and this should be kept in mind when comparing findings between articles. For

[8] Coronavirus (COVID-19) booster vaccination | The coronavirus (COVID-19) vaccine (nhsinform.scot)

example, some studies have looked at vaccine efficacy after one dose only whereas others have looked at vaccine efficacy after two or three doses. The studies also use different methodologies and sampling approaches and this will also influence the findings. Please also note some of the studies referenced are pre-prints. This means they have not yet been peer-reviewed (evaluated for robustness by other academics in the same field) or published, and any findings should be considered more cautiously. Pre-prints have been highlighted where relevant. The full version of the bibliography can be found in Annex A.

6. Overview of Vaccine Efficacy findings

6.1 Overall, the findings of the studies included in Annex A suggest that vaccine efficacy for the Highest Risk List is not as high after the initial two doses as for the general population, with a number of articles recommending booster and/or third doses as well as continued non-clinical safety measures (e.g. face masks and social distancing) to protect the health and wellbeing of immunocompromised people. Some studies have also looked at what characteristics are associated with increased risk for adverse COVID-19 outcomes, with several Highest Risk List subgroups highlighted as well as characteristics such as being older, male, or living in a care home.

6.2 A number of studies included here have also looked at differences between vaccine types (mainly AstraZeneca, Pfizer, and Moderna) but statistical significance testing has not been carried out in all studies which means any differences are at this stage only observed and it is not clear whether the differences are coincidental or not.

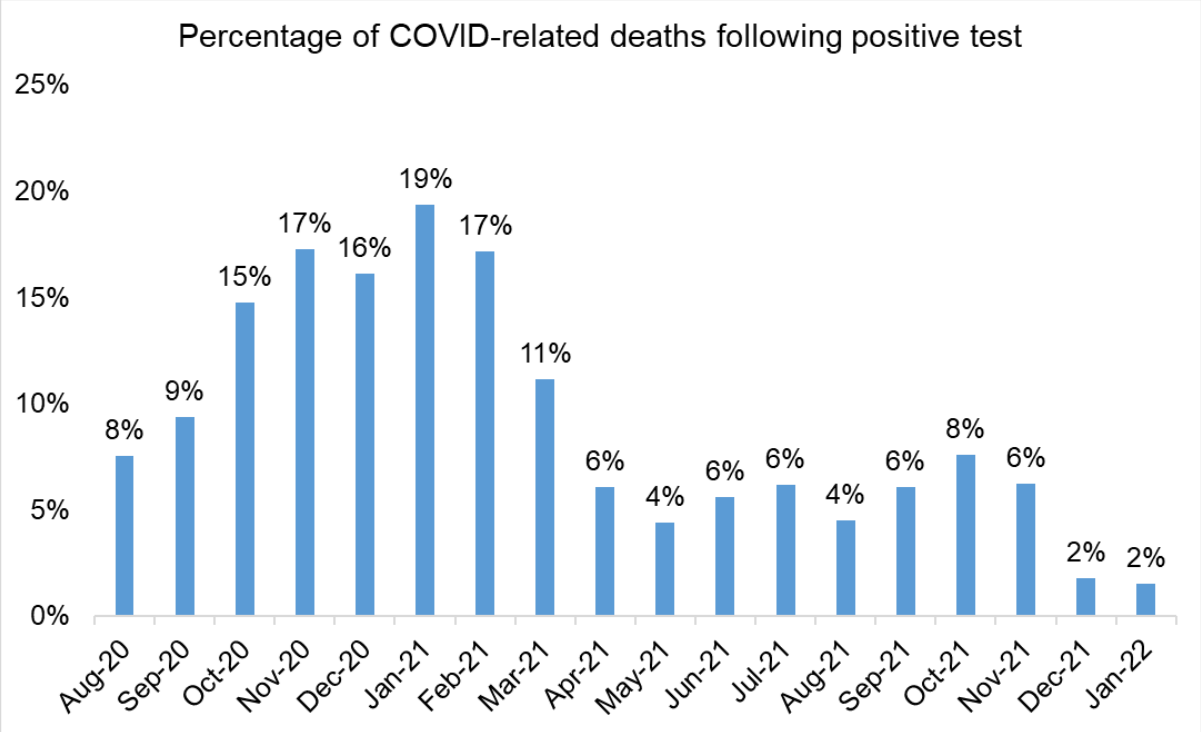
6.3 A recent study[9] estimated that the Omicron variant was substantially less likely to result in COVID-19 hospitalisation than Delta. It also found that a third/booster dose of a COVID-19 vaccine offered substantial additional protection against symptomatic disease within two weeks of this additional dose, compared to two doses of vaccine received 25 or more weeks ago. This protection was greatest for Delta, but still substantial for Omicron.

7. Percentage of COVID-19 deaths in the Highest Risk List

7.1 We have seen a decrease in the total percentage of Highest Risk List COVID-related deaths following a positive test since the roll-out of the vaccination programme in December 2020. Nineteen per cent of people on the Highest Risk List with a positive COVID test sadly died from COVID-related causes in January 2021, however that percentage has continued to decrease and as of January 2022 was at 2%, as shown in figure 4 below.

[9] Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland — University of Edinburgh Research Explorer

Figure 2 - Percentage of COVID-related deaths in the Highest Risk List following positive test.



7.2 We know there has been a significant reduction in the number of COVID-related deaths across all groups within the Highest Risk List since the roll-out of Scotland's vaccination programme, as highlighted in Figure 7.

7.3 We do not know if those dying of COVID-related causes were vaccinated but, as of 31 January 2022, 97% of the Highest Risk List had received at least one vaccine dose, 96% had received two doses and 90% had received a booster or a third dose.

7.4 Further evidence on COVID-related deaths is available in Annex B.

Medical specialists consultation and feedback for the review

8. Throughout the COVID-19 pandemic the Scottish Government regularly consulted with medical experts to seek their clinical perspective and views in order to support the continuation of safe, effective, person-centred and sustainable advice for people on the Highest Risk List. These experts recognise:

- Vaccination has been a critical component in preventing severe illness and death associated with COVID-19, including for those at highest risk
- The availability and effectiveness of new treatments such as antivirals and monoclonal antibodies mean we are now able to take a different approach to supporting those at highest risk

- Death rates as a result of COVID-19 amongst people on the Highest Risk List are now significantly lower
- There is now a far better understanding of the impact of COVID-19 on those with specific clinical conditions and the risk factors that may put someone at increased risk of becoming seriously unwell from COVID-19
- Asking people to isolate away from friends, family and society in general had a substantial negative impact on people psychologically and socially
- Evidence clearly points to the reduced clinical risk for the majority of people on the Highest Risk List, however, there are people who continue to have a higher risk from COVID-19 post vaccination, primarily people whose immune systems are suppressed or compromised due to a health condition or treatment
- Consideration should be given to ways of identification and support in the future for people who may continue to be at highest risk, taking into account potential new variants and emerging evidence

8.1 As part of those ongoing discussions for the Highest Risk List, the Scottish Government and medical experts considered the data and agreed it reasonable to now retire the Highest Risk List. They went on to add:

- Asking people on the Highest Risk List to follow the general population advice, unless otherwise stated by their GP and clinician, is appropriate
- A future identification process is needed to allow for the rapid identification of individuals to be prioritised for vaccination, for treatments and, if the threat level increases, for additional protective advice
- Clear communication on the change is needed to ensure individuals have a clear understanding of the reasons for retiring the Highest Risk List

Review of groups

9. A systematic approach was taken to reviewing the information available resulting in the retiring of the Highest Risk List and taking account of the needs for support for those individuals who have a residual risk post-vaccination. A full summary of the review of groups is included in Annex C.

9.1 The general principles below informed the review and provide a clear path to retiring the Highest Risk List.

Evidence	is informed by the best available evidence.
Data	uses data which monitors trends and supports progress.
Engagement	is understood by people on the HRL, clinicians and providers of secondary and third care and support, through a clear communication strategy detailing the rational for retiring the list, including ongoing support available.
Risk	is informed by residual post vaccination risk.
Benefit	shifts the approach from broad universal measures and actions to strategies targeted towards newly defined higher risk group/s.

Findings of the review

10. It is clear from the review that the Highest Risk List is not serving the same purpose as when it was created in March 2020. Highest risk individuals have been advised to follow the same advice as the general population since August 2021 (with the exception of attending work in level 4), and no additional clinical advice has been given by the Scottish Government since this date.

10.1 There is strong evidence to show that vaccines are offering significant protection to people on the Highest Risk List, including people who are immune-suppressed or immune-compromised from becoming severely ill or dying.

10.2 There has been a significant reduction in the number of deaths from COVID-19 across all groups within the Highest Risk List, since the roll-out of Scotland's vaccination programme.

10.3 The majority of those previously identified as highest risk do not face the same level of risk of severe illness or death from COVID-19 following the vaccination roll-out and introduction of therapeutic treatments.

10.4 Retiring of the Highest Risk List requires consideration of how we identify highest risk individuals quickly for access to therapies, treatments, priority vaccination or advice when needed and based on eligibility criteria in the future.

10.5 If a variant of concern were to arise, or the threat level was to rise significantly and tailored non-pharmaceutical advice was required, the Highest Risk List in its current form raises a risk of inaccuracy and would not be appropriate in identifying highest risk individuals due to it not being clinically revalidated following changes in risk factors.

Conclusions

11. The pandemic context is very different now to when the Shielding or Highest Risk List was first introduced. The factors that now identify someone as being at highest risk from COVID-19 have changed.

11.1 Furthermore, as the number of people who have been vaccinated rises, the population overall benefits from greater protection against the serious effects of the virus, including those on the Highest Risk List, and the very small number of people who cannot be vaccinated due to allergy to ingredients or previous serious reaction to the vaccine.

11.2 For some time now, we have advised people on the Highest Risk List to follow the same advice and guidance as the rest of the population unless advised otherwise by their GP and clinician.

11.3 We do not intend to advise those who may be at highest risk to return to shielding in the future given the strong evidence of the detrimental impact of isolation on physical and mental health and wellbeing. Therefore the Highest Risk List no

longer serves the purpose it was created for. For that reason we are now in a position to retire the Highest Risk List.

11.4 Following the roll out of Scotland's Vaccination Programme the decision to retire the Highest Risk List has been reached by consensus across all Scottish Government clinical advisors. The evidence shows that clinical risk of serious outcomes from COVID-19 is reduced thanks to the vaccination programme and new treatments.

11.5 Given the wide range of circumstances and health conditions of people on the Highest Risk List, ensuring personalised advice and support is available to each individual on the list is an important part of this transitional period. GPs and clinicians who best know the circumstances of people at highest risk will continue to be the first port of call for individual clinical advice.

11.6 It is recognised there are some people on the Highest Risk List who currently have conditions that prevent a robust vaccination response, or who take medication that has a similar immune-suppressing effect. These individuals have always been at risk and, pre-pandemic, would have had to make individual risk assessments in consultation with their clinician.

11.7 As we transition beyond the current Highest Risk List we will adopt an identification process to be able to rapidly and accurately identify people who should be prioritised for vaccination, for treatments and, if the threat level increases, for additional protective advice.

11.8 The retirement of the Highest Risk List applies to all groups previously identified as being at highest risk as we return to the pre-pandemic approach of individual clinical advice for those who may need to take extra precautions (for example people who are immuno-suppressed), just as they would have done before the pandemic to keep themselves safe from other viruses and disease.

11.9 Our overall strategic approach going forward is to support and protect people who are at higher risk from COVID-19. While the threat from COVID-19 is currently waning and we lift legal restrictions as a result, we know that many people at highest risk may be anxious.

11.10 Clear communication is required to support the transition of those on the Highest Risk List to fully participate in society again. This will include;

- The Scottish Chief Medical Officer writing out to all individuals on the Highest Risk List to inform them their risk of severe illness or death from COVID-19 is now reduced following vaccination and treatments and explaining the clinical context behind that decision, with confirmation of the retirement of the Highest Risk List

- Clear guidance to key stakeholders of the Highest Risk List such as health charities, local councils and voluntary sector organisations setting out what factors may make an individual more vulnerable, and signposting to available evidence

Annex A - Vaccine Efficacy and Effectiveness in people on the Highest Risk List: Evidence Summary

12. Vaccine Efficacy: Annotated Bibliography

12.1 The following section is an annotated bibliography of relevant studies on vaccine efficacy that have informed the current Scottish Government COVID-19 Highest Risk policy. It includes brief summaries of the main findings and their key limitations. Limitations are factors or characteristics which may have influenced or impacted study findings in particular ways. Many studies in this annotated bibliography will have several limitations. This does not necessarily mean that the studies are fundamentally wrong. Instead, limitations highlight things readers should keep in mind when interpreting findings.

12.2 This is not a complete list of studies on vaccine efficacy for the Highest Risk List. It is only a list of studies that have informed Scottish Government policy. Readers should note that studies included in this list measure different things and this should be kept in mind when comparing findings between articles. For example, some studies have looked at vaccine efficacy after one dose only whereas others have looked at vaccine efficacy after two or three doses. The studies also use different methods and samples and this will also influence the findings. Please also note some of the studies referenced are pre-prints. This means they have not yet been peer-reviewed (evaluated for robustness by other academics in the same field) or published, and any findings should be considered more cautiously. Pre-prints have been highlighted where relevant.

13. Vaccine Efficacy and Effectiveness: Overview of annotated bibliography findings

13.1.1 Overall, the findings of the studies included suggest that vaccine efficacy for the Highest Risk List is not as high as for the general population, with a number of articles recommending booster and/or third doses as well as continued non-clinical safety measures (e.g. face masks and social distancing) to protect the health and wellbeing of more immunocompromised people.

13.1.2 Some studies have also looked at what characteristics are associated with increased risk for adverse COVID-19 outcomes, with several Highest Risk List subgroups highlighted as well as characteristics such as being older, male, or living in a care home.

13.1.3 A number of studies included here have also looked at differences between vaccine types (mainly AstraZeneca, Pfizer, and Moderna) but statistical significance testing has not been carried out in all studies which means any differences are at this stage only observed and it is not clear whether the differences are coincidental or not.

13.2 **Agrawal, U., Vittal Katikireddi, S., McCowan, C., Mulholland, RH., Azcoaga-Lorenzo, A., Amele, S., Francis Fagbamigbe., A., Vasileiou, E., Grange, Z., Shi, T., Kerr, S., Moore, E., Murray, JLK., Ahmar Shah, S., Ritchie, L., O'Reilly, D., Stock, SJ., Beggs, J., Chuter, A., Torabi, F., Akbari, A., Bedston, S., McMenamin, J., Wood, R., Tang, RSM., de Lusignan, S., Hobbs, R., Woolhouse, M., Simpson, CR., Robertson, C., and Sheikh, A. (2021) 'COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2.57 million people in Scotland (EAVE II): a prospective cohort study'.**
The Lancet. **Online First.**

This national-level study looked at the frequency of COVID-19-related hospitalisations and deaths in people who had received at least one vaccine dose in Scotland and sought to establish what characteristics put people more at risk of hospitalisation or death based on this. The research period for this study was 8th December 2020 to 18th April 2021.

The study found that out of the 2,572,008 people who received their first vaccine dose during the study period, less than 0.1% were hospitalised or died due to COVID-19 14 days or more after vaccination.

The analysis also found that, after vaccination, COVID-19-related hospitalisation and death continued to be associated with:

- older age (≥80),
- having more than one comorbidity (more than one disease or condition present in the same person at the same time),
- being hospitalised in the previous four weeks,
- care home residence,
- socio-economic deprivation,
- being in a high-risk occupation (number of previous COVID-19 tests were used as a proxy for high-risk occupational groups who were repeatedly tested),
- being male,
- or being an ex-smoker.

Looking at people with multiple comorbidities, Agrawal et al. found that, for people who had been vaccinated, a history of:

- asthma,
- chronic kidney condition,
- heart failure,
- type 2 diabetes,
- dementia,
- or coronary heart disease

was associated with increased risk of hospitalisation or death.

The study suggested that, for those who had received the Pfizer vaccine, there was no association between increased risk of hospitalisation or death and asthma or heart failure. However, the study was unable to make robust comparisons between vaccines due to their differential use. This finding should therefore be considered cautiously.

13.3 **Boyarsky, BJ., Werbel, WA., Avery, RK., Tobian, AAR., Massie, AB., Segev, DL., and Garonzik-Wang, JM. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. *JAMA*. 325(17).**

This American study investigated immune responses following the first vaccine dose in solid organ (organs that are not hollow or liquid, such heart, liver, kidney, and lungs, among others) transplant recipients. The research period for this study was 16th December 2020 to 5th February 2021. Participants (n=436) were recruited via social media, meaning this study did not use a representative sample.

The study found that antibodies developed in 17% of participants 20 days after the first vaccine dose. The analysis also suggested that patients who were receiving anti–metabolite maintenance immunosuppression therapy (medication designed to prevent organ transplant rejections) were less likely to develop antibodies than those not receiving this therapy (37% vs 63%). Older transplant recipients were also less likely to develop antibodies. The study also suggested that those receiving the Moderna vaccine were more likely to develop antibodies than those receiving Pfizer (69% vs 31%).

A key limitation of this study is its convenience sample which means it may not apply to a wider population. The study also lacked a control group without immunosuppression, and it should also be noted the analysis is of responses to the first vaccine dose only. Despite these limitations, it was useful to highlight the potential issue caused by immunosuppression. This study suggested that vaccine efficacy was reduced in the solid organ transplant group.

13.4 **Grange, Z., Buelo, A., Sullivan, C., Moore, E., Agrawal, U., Bouhkhari, K., McLaughlan, I., Stockton, D., McCowan, C., Robertson, C., Sheikh, A., and Murray, JLK. (2021) Characterisation and risk of COVID-19 related death in fully vaccinated people in Scotland. The Lancet. Online First**

This national-level study sought to estimate the frequency of COVID-19-related deaths in fully vaccinated people in Scotland and to describe characteristics associated with this. This study looked at people who had been fully vaccinated (i.e. those who had had two vaccination doses) by 18th August 2021. At the time of the study, there had been 236 COVID-19-related deaths in fully vaccinated people (those who had received at least 2 doses of vaccine)..

The study found most people who died after full vaccination were older than 75, with a median age of 80. The study also found that men had a higher risk of COVID-19 death than women, and that people with five or more comorbidities (more than one disease or condition present in the same person at the same time), were at

substantially higher risk (although the confidence intervals for this were wide, which means the finding is uncertain).

As the study found that COVID-19-related deaths following vaccination were uncommon, there was only a small number of deaths to analyse, and findings should therefore be considered cautiously. The authors stressed the importance of continued caution and use of non-pharmaceutical interventions, particularly for older adults with multiple comorbidities. This study suggested that older people, men, and people with several pre-existing risk conditions were at increased risk of COVID-19 related death following vaccination.

13.5 **Hall, VG. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. NEJM. 385(13)**

This letter to the editor details the results of a double-blind randomised controlled trial (n=120) of a third dose of the Moderna vaccine compared with a placebo in transplant recipients. This study was carried out between 25th May and 30th August 2021.

The study found that a third dose of the Moderna vaccine in transplant recipients had a substantially higher antibody response than the placebo. 55% of the third dose group (n=60) had the study design's pre-requisite antibody level after four months, compared to 18% of the placebo group (n=57). The author recommends that a third-dose booster vaccine dose should be considered for transplant recipients who have received two doses of Moderna.

This study had a relatively small sample size and the author acknowledges the pre-requisite antibody level set was arbitrary and not necessarily predictive of protection from infection. This article suggested that a third dose of the Moderna vaccine had a benefit in increasing immune (antibody) responses for transplant recipients.

13.6 **Hippisley-Cox, J., Coupland, CAC., Mehta, N., Keogh, RH., Diaz-Ordaz, K., Khunti, K., Lyons, RA., Kee, F., Sheikh, A., Rahman, S., Valabhji, J., Harrison, EM., Sellen, P., Haq, N., Semple, MG., Johnson, PWM., Hayward, A., and Ngyen-Van-Tam, JS. (2021) 'Risk prediction of COVID-19 related death and hospital admission in adults after COVID-19 vaccination: national prospective cohort study'. BMJ. 374 (2244).**

This national-level study analysed COVID-19-related hospitalisations and deaths after vaccination in England in order to identify risk factors. The study period for this project was 8th December 2020 to 15th June 2021. The study included people who had only one vaccine dose as well as those who had had both doses.

Analysis identified the highest risks for COVID-19-related mortality as being associated with:

- Down's syndrome
- kidney transplants
- sickle cell disease
- living in care homes
- chemotherapy

- ever having had a solid organ transplant
- having recently had a bone marrow transplant
- HIV/AIDS
- dementia
- Parkinson's Disease
- neurological conditions
- liver cirrhosis

It also found COVID-19 mortality increased with:

- age and deprivation
- being male
- being of Indian and Pakistani ethnic origin

The trends for COVID-19 related hospitalisations were similar. It should be noted that numbers for some of the subgroups were small. In addition to this, most of the data was based on only one vaccine dose, with a relatively small proportion of COVID-19 deaths occurring in those who had had both vaccine doses.

There was also a lack of data on younger people without underlying conditions due to the prioritisation of the national vaccine roll-out. This study suggested that there was a higher risk of COVID-19 related death or hospitalisation following at least one vaccination dose for people who:

- had relevant pre-existing medical conditions that make them more vulnerable to hospitalisation or death from COVID-19
- were older
- lived in more deprived areas
- were of Indian or Pakistani origin

13.7 **Kearns, P., Siebert, S., Willicombe, M., Gaskell, C., Kirkham, A., Pirrie, S., Bowden, S., Magwaro, S., Hughes, A., Lim, Z., Dimitriadis, S., Murray, SM., Marjot, T., Win, Z., Irwin, SL, Meacham, G., PITCH Study Group, OCTAVE Study Group, Alex G. Ritcher, Kelleher, P., Satsangi, J., Miller, P., Rea, D., Cook, G., Turtle, L., Klenerman, P., Dunachie, SJ., Basu, N., de Silva, TI., Thomas, D., Barnes, E., Goodyear, CS., and McInnes, I. Examining the immunological effects of COVID-19 vaccination in patients with conditions potentially leading to diminished immune response capacity – the OCTAVE Trial. PRE-PRINT. Accessed on 4th November 2021.**

NB. This study is a pre-print and has not been peer-reviewed. Findings should therefore be considered cautiously until it has been appropriately reviewed and approved for publication.

The OCTAVE trial is a national-level study into vaccine responses within and between different disease cohorts from across the UK. This paper reports on analysis based on the first 655 patients as of 13th August 2021 and also includes data from 231 healthy individuals as a control group.

The study found that 89% of patients with less good immune systems produced antibodies after vaccination, compared to 100% of tested healthy individuals. People

with particular conditions were less likely to produce antibodies, e.g. ANCA-Associated Vasculitis (72%), end stage kidney disease requiring haemodialysis with immunosuppression (17%), and hepatic disease (17%).

Of the patients that did produce antibodies after vaccination, 40% across the different disease cohorts still produced lower levels of antibodies than the healthy subjects. However, it should be noted that the tested healthy subject sample was relatively small (n=93).

There were various limitations to this study, including not carrying out formal statistical comparison between groups, an inability to obtain baseline data on all participants, disease group sizes being unequal, and the control group and disease cohort samples were not equivalent in terms of both gender and age, so comparisons of outcomes may not be accurate.

This study suggested that immunocompromised people were less likely to produce an immune response to the COVID-19 vaccine than the general population and were also more likely to produce a lower response.

13.8 **McKeigue, PM., McAllister, DA., Bishop, J., Hutchinson, S., Robertson, C., Lone, N., McMenamin, J., Goldberg, D., and Colhoun, HM. et al (2021) Efficacy of COVID-19 vaccination in individuals designated as clinically extremely vulnerable in Scotland [version 1; peer review: 1 not approved]. F1000Research 10(663). PRE-PRINT. Accessed 5th November**
NB. This study is a pre-print and has not been peer-reviewed. Findings should therefore be considered cautiously until it has been appropriately reviewed and approved for publication.

This matched case-control study estimated vaccine efficacy in reducing the risk of severe COVID-19 (defined as entry to critical care or death) in people designated clinically extremely vulnerable in Scotland. The study period for this research was 1st December 2020 to 16th March 2021.

The study found that the efficacy of a single vaccination dose against severe COVID-19 was as high for people designated as clinically extremely vulnerable as for those who were not. However, this study is limited by small numbers of data for specific risk conditions, especially for solid organ transplant recipients who are at highest risk. The study was therefore unable to reliably estimate the vaccine efficacy for transplant recipients.

This study suggested vaccine efficacy was as high for those who were clinically extremely vulnerable as for the general population, but did not reliably take into account vaccine efficacy for transplant recipients and other specific risk conditions.

13.9 **McKeigue, PM., McAllister, DA., Hutchinson, SJ., Robertson, C., Stockton, D., and Colhoun, HM. (2021) Efficacy of vaccination against severe COVID-19 in relation to Delta variant and time since second dose: the REACT-SCOT case-control study. PRE-PRINT – Accessed 3 November 2021**

NB. The study linked is a pre-print and had not been peer-reviewed at time of writing. Findings should therefore be considered cautiously until it has been appropriately reviewed and approved for publication.

This national-level case-control study investigated vaccine efficacy against severe COVID-19 (defined as entry to critical care or death) since the Delta variant became dominant in Scotland, and looked at whether vaccine efficacy waned with time. The study considered all diagnosed cases of COVID-19 in Scotland up to 19 August 2021.

The study found that the replacement of the Alpha variant by the Delta variant as the dominant COVID-19 variant in Scotland in May 2021 was accompanied by a temporary reduction of vaccine efficacy against severe COVID-19. This finding does not suggest that vaccines are less effective for the Delta variant, however it should be noted that authors did not have a direct measurement for variant types and instead looked at the time windows for replacement of the Alpha variant by the Delta variant.

The study also showed that two doses of AstraZeneca was 91% effective against severe disease, however this decreased to 69% at 20 weeks from the second dose. The efficacy for Pfizer and Moderna was measured as 92%, declining in the first ten weeks after second dose to then stabilise at around 90%.

Based on these findings, authors recommend that booster vaccine doses should initially focus on those who received the AstraZeneca vaccine. The authors note that the findings may be affected by a seasonality bias as analysis is based on cases between May 2021 and August 2021. This means that the findings may not be accurate for other times of year. This study suggested that COVID-19 vaccines are effective against the Delta variant, and that the AstraZeneca vaccine efficacy decreases substantially with time after the second dose.

13.10 **McKeigue, PM., McAllister, DA., Robertson, C., Hutchinson, S., McGurnaghan, S., Stockton, D., and Colhoun, HM. Efficacy of two doses of COVID-19 vaccine against severe COVID-19 in those with risk conditions and residual risk to the clinically extremely vulnerable: the REACT-SCOT case-control study. PRE-PRINT. Accessed 4 November 2021.**
NB. This study is a pre-print and has not been peer-reviewed. Findings should therefore be considered cautiously until it has been appropriately reviewed and approved for publication.

This national-level study sought to determine whether the efficacy of the COVID-19 vaccine varied with clinical risk categories as well as to investigate the risk factors for severe COVID-19 (defined as cases with entry to critical care or death) after receiving two vaccine doses in Scotland. The study period for this research was 1st December 2020 to 19th August 2021.

The study found that vaccine efficacy against severe COVID-19 following two vaccine doses was 73% for those designated as clinically extremely vulnerable, compared to 89% for those with moderate risk conditions and 94% for people without risk conditions.

The study also found that, among the double-vaccinated population at time of analysis, those with designated risk conditions or who are clinically extremely vulnerable accounted for 85% of severe cases and 75% of hospitalised cases. It should be noted that this refers to small numbers of deaths and hospitalisations – at the time of study there had been 81 deaths and 71 hospitalisations in the fully vaccinated population (n= 5,150,310) at least 14 days after vaccination.

The study findings suggested that solid organ transplant patients were most at risk of severe disease out of the double-vaccinated clinically extremely vulnerable group, but authors noted that even in this subgroup the absolute risk of severe COVID-19 was low. Numbers for some of the clinically extremely vulnerable groups were small. The authors recommended passive immunisation therapies for solid organ transplant recipients and suggested a booster-dose for added protection. This study suggested vaccine efficacy was lower for those who were clinically extremely vulnerable and those who had moderate risk conditions compared to people without risk conditions.

13.11 **Prendecki, M., Thomson, T., Clarke, L., Martin, P., Gleeson, S., Cardoso De Aguiar, R., Edwards, H., Mortimer, P., McIntyre, S., Mokreri, D., Cox., A., Pickard., G., Lightstone. L., Thomas, D., McAdoo, SP., Kelleher, P., and Willicombe, M. (2021) 'Immunological responses to SARS-CoV-2 vaccines in kidney transplant recipients'. The Lancet. 398(10310).**

This study investigated antibody responses to two doses of the Pfizer and AstraZeneca vaccines in two groups of kidney transplant recipients (n=920 and n=106) and one group of healthcare workers (n=65).

The study found that people who had not had COVID-19 and who received the Pfizer vaccine were more likely to produce antibodies and develop higher levels of antibodies in the blood compared to patients receiving AstraZeneca. It also found that the immune (antibody) responses in transplant recipients were significantly weaker than those seen in health-care workers. As the study cohorts were imperfectly matched both in terms of size and other characteristics such as age, this conclusion should be considered with caution, which is acknowledged by the authors. The study recommended that kidney transplant patients' household members should be immunised and that patients should be educated to maintain physical distancing rules. This study suggested that vaccine efficacy was not as high for kidney transplant recipients as for health care workers who had not had transplants.

13.12 **Sheikh, A, Kerr, S, Woolhouse, M, McMenamin, J & Robertson, C. (2021) Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. PRE-PRINT. Accessed 25 February 2022.**
NB. This study is a pre-print and has not been peer-reviewed. Findings should therefore be considered cautiously until it has been appropriately reviewed and approved for publication.

This national-level study used the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) Scotland-wide prospective cohort to estimate hospital admissions associated with omicron and vaccine effectiveness against symptomatic disease with the omicron variant. The analysis covered the period from 1st November to 21st December 2021.

The study estimated that the Omicron variant was substantially less likely to result in COVID-19 hospitalisation than Delta. It also found that a third/booster dose of a COVID-19 vaccine offered substantial additional protection against symptomatic disease within two weeks of this additional dose, compared to two doses of vaccine received 25 or more weeks ago. This protection was greatest for Delta, but still substantial for Omicron.

The study had a number of limitations. Firstly, challenges with the data meant that the study was unable to establish the effectiveness of the vaccine in protecting against symptomatic disease for those who tested positive for COVID-19 in hospital settings. Secondly, the study assumed that the length of time between contracting COVID-19 and ending up in hospital because of COVID-19 would be the same for both the delta and omicron variants.

The low number of hospital admissions for COVID-19 during the study period made it difficult to accurately predict future hospital admission rates from the available data. Finally, there is also a possibility that the effectiveness of the vaccine would wane over time for certain groups in the population. The timing of this study meant that the research was unable to assess this.

13.13 **Sheikh, A., McMenamin, J., Taylor, B., and Robertson, C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. The Lancet. 397(10293).**

This national-level study explored the risk of hospitalisation for COVID-19, estimated vaccine effectiveness in preventing COVID-19 hospitalisation and described the demographic profile of COVID-19 patients. It also looked at differences according to COVID-19 variant. The analysis covered the period from 1st April to 6th June 2021.

The study found that for the whole population cohort, the Pfizer vaccine offered very good protection at least 14 days after the second dose (92% for the Alpha variant, and 79% for the Delta variant). The AstraZeneca vaccine was also protective but with reduced effect (73% for the Alpha variant, and 60% for the Delta variant).

However, the study did not test whether the difference between vaccines was statistically significant, so the finding should be considered cautiously. The study also found that the Delta variant was found mainly in younger, more affluent groups, and that the risk of COVID-19 hospitalisation approximately doubled in those with the Delta variant compared to those with the Alpha variant, with the risk of hospitalisation particularly increased in those with five or more relevant comorbidities (more than one disease or condition present in the same person at the same time).

This study suggested that vaccines offered good protection for the general population as a whole against COVID-19 related hospitalisation.

Annex B - Highest Risk List Mortality and Deaths Data[10]

14. Since the start of the COVID-19 outbreak, Public Health Scotland (PHS) has been working closely with Scottish Government and health and care colleagues to monitor COVID-19 amongst the population. This section presents analysis based on the latest published PHS figures (as at 21 February 2022) on COVID-19-related deaths for the Highest Risk List in Scotland[11]. Comparisons are made with mortality rates for the rest of the population. Levels of excess mortality due to COVID-19 within the Highest Risk List cannot be easily established as there is no similar cohort pre-COVID-19 pandemic to compare against.

14.1 As at 21 February 2022, there were 177,475 individuals on the Highest Risk List in Scotland. This equates to around 3.2% of the Scottish population. The table below (Figure 5) shows the number and rate per 100,000 population of individuals on the Highest Risk List by age group and sex. Fifty-one per cent of people on the Highest Risk List are aged 65 and over, and 56% are women.

Figure 3 - Number and rate per 100,000 population of individuals on highest risk list by age group and sex. There are 33 individuals whose age is unknown.

Age Group (years)	Male	Female	Total	Rate of individuals on the HRL per 100,000 population
0 to 4	143	149	292	111
5 to 12	426	313	739	154
13 to 15	197	156	353	204
16 to 24	1,825	1,726	3,551	626
25 to 34	3,711	4,326	8,037	1,070
35 to 44	5,287	6,955	12,242	1,800
45 to 54	9,346	12,882	22,228	2,992
55 to 64	17,190	22,777	39,967	5,315
65 to 69	10,020	12,430	22,450	7,473
70 to 79	20,153	23,268	43,421	8,971
80+	10,247	13,915	24,162	8,896
All	**78,545**	**98,897**	**177,442**	**3,246**

[10] Deaths involving the novel coronavirus COVID-19 (SARS-CoV-2) are defined as those where COVID-19 is mentioned by the certifying doctor on the death certificate, either as the underlying cause of death or as a contributory cause. The relevant ICD-10 codes for these causes of death are U07.1, U07.2, U09.9 and U10.9.
Deaths involving coronavirus (COVID-19) in Scotland : Methodology Guide (nrscotland.gov.uk)
[11] COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

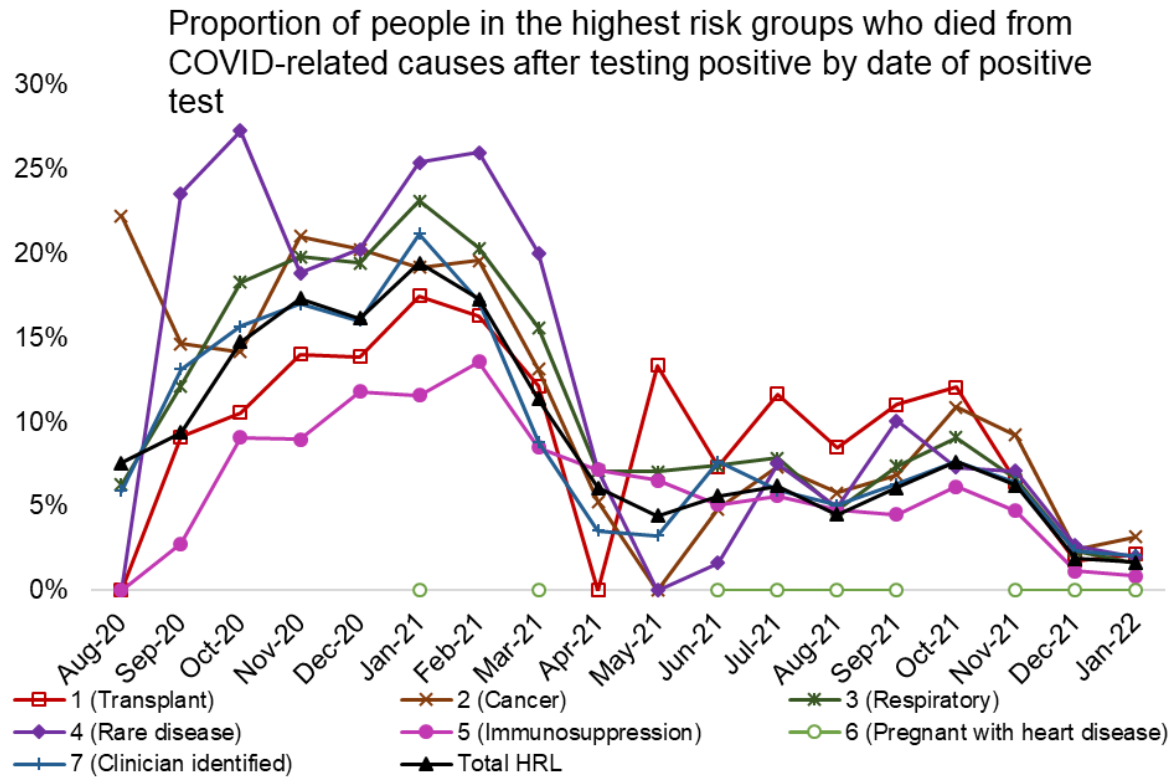
15. COVID-19 deaths in the Highest Risk List

15.1 In January 2022, COVID-related deaths in the Highest Risk List accounted for 25% of all COVID-related deaths in Scotland. This has decreased in the last few months from 39% in June 2021 (although the latest figures may rise as deaths are identified as being in the Highest Risk List).

15.2 The proportion of people on the Highest Risk List dying of COVID-related causes within 28 days after a positive test fell from a high of 19% in January 2021 to 6% by April 2021 (figure 6) and it remained around this level until December 2021[12] when it dropped further to 2% (the lowest in the time series).

15.3 We do not know if those dying of COVID-related causes were vaccinated, but as of 31 January 2022, 97% of the Highest Risk List had received at least one vaccine dose, 96% had received two doses and 90% had received a booster or a third dose. This fall in COVID-related deaths may support findings from studies such as Kearns et al and McKeigue et al that suggest COVID-19 vaccinations do produce antibodies and offer some protection for people on the Highest Risk List, albeit on a reduced level compared to the general population.

Figure 4 - Proportion of people on the highest risk groups who died from COVID-related causes within 28 days after a positive test.

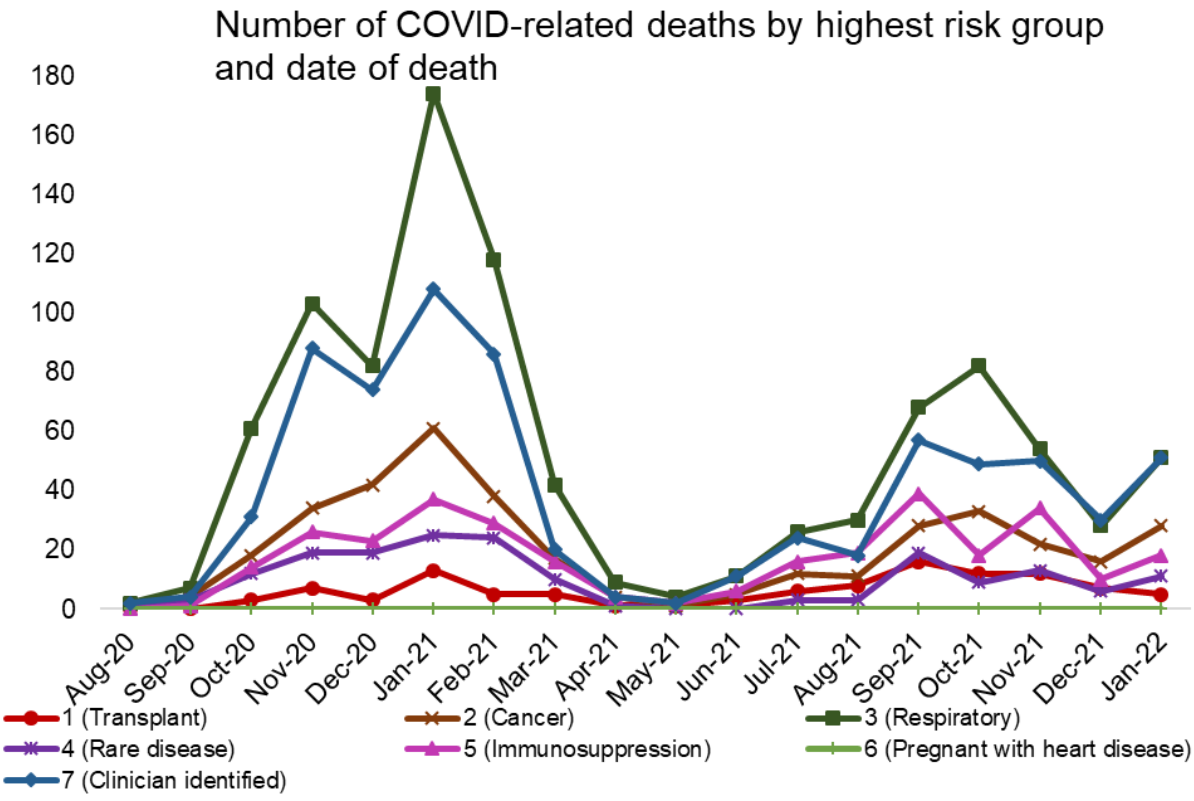


***Please note where there are gaps in a series, no-one from that group tested positive.**

[12] On 5th January 2022 Scotland introduced a revised testing strategy and asymptomatic positive lateral flow device (LFD) test results were not required to perform a PCR test. The figures presented here for total positive tests include those who had a positive LFD only, a positive PCR only and those who had both a positive LFD and positive PCR.

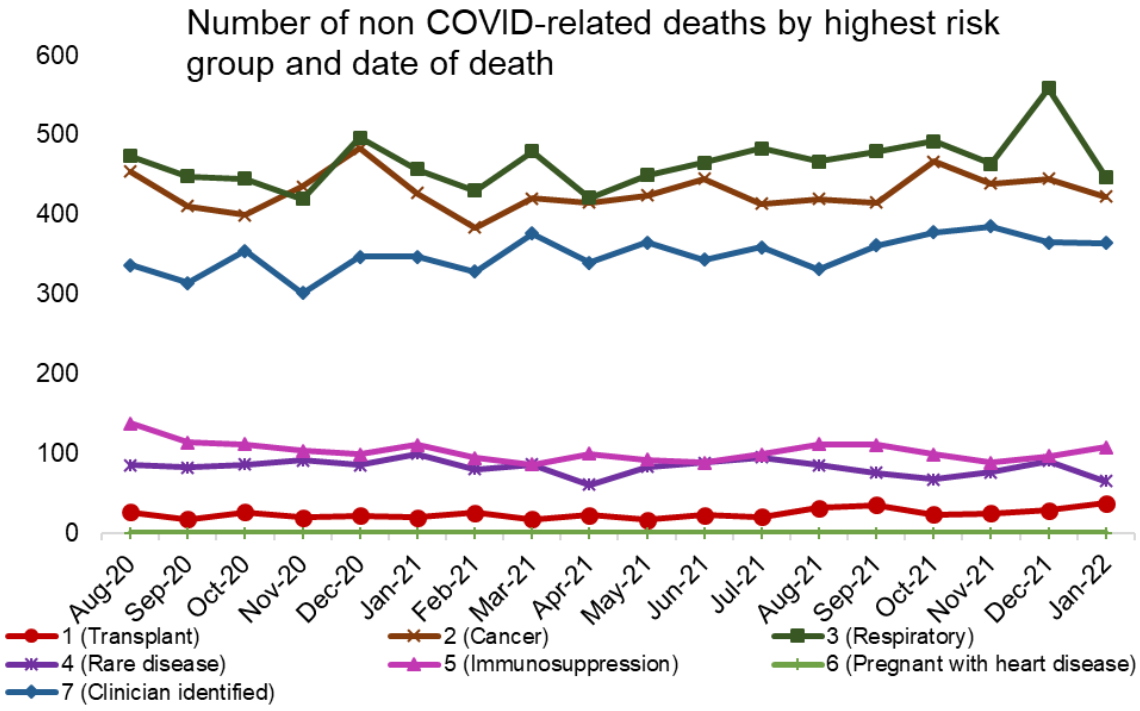
15.4 The number of COVID-related deaths amongst the Highest Risk List in Scotland remains highest for those in the respiratory and clinician identified groups. It is lowest for pregnant with heart disease (where there have been no deaths) and in the transplant group (figure 7).

Figure 5 - COVID-related deaths by highest risk group and date of death.



15.5 A similar pattern is seen for non COVID-related deaths (figure 8), with the exception of the cancer group which has the second highest number of non COVID-related deaths compared to the third highest number of COVID-related deaths.

Figure 6 - Non COVID-related deaths by highest risk group and date of death.

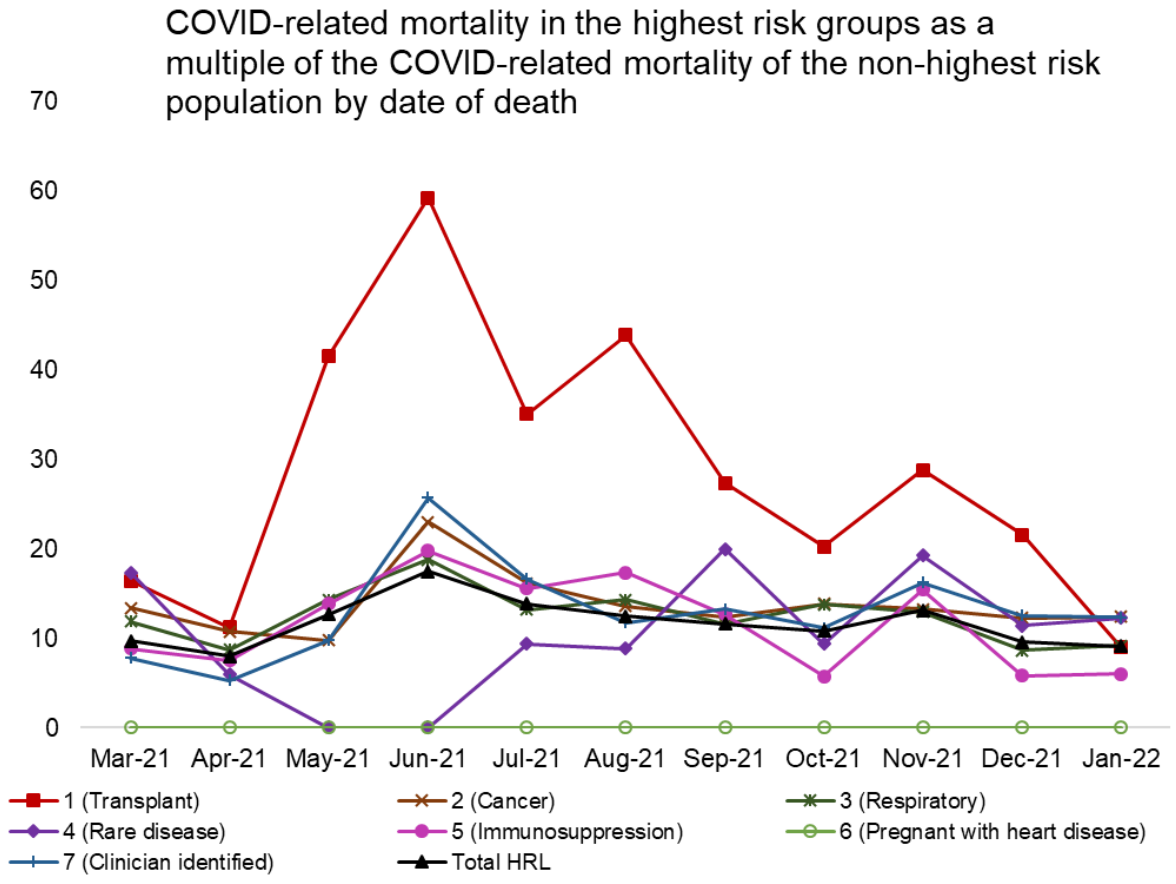


16. COVID-19 mortality rates in the Highest Risk List

16.1 The Highest Risk List as a whole had a COVID-19 mortality rate 9 times higher than the non-Highest Risk List population in January 2022 (figure 9). This supports annotated bibliography findings that suggest that there remains an increased risk of COVID-19 mortality for the Highest Risk List after vaccination compared to the general population. The COVID-19 mortality ratio has fallen in the last few months from 17 times higher in June 2021 (highest in the time series).

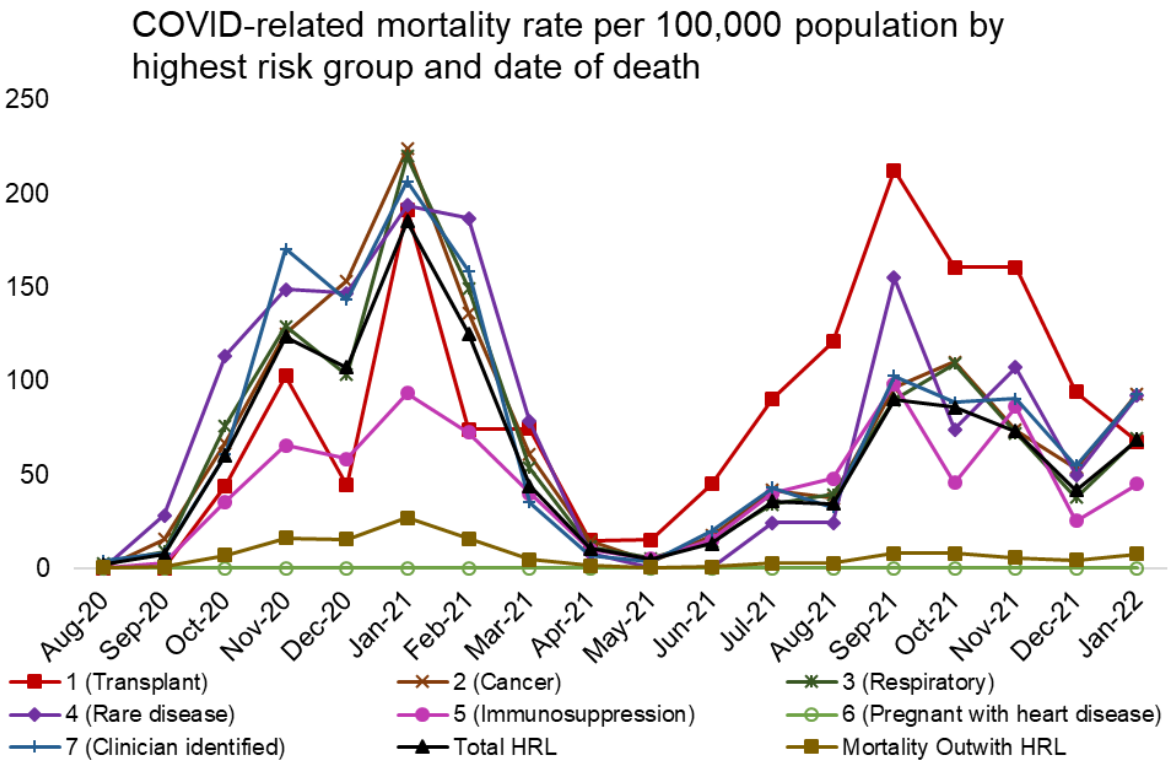
16.2 In January 2022, the cancer, rare diseases and clinician identified groups had the highest relative COVID-related mortality rate at 12 times higher than the non-Highest Risk List population.

Figure 7 - COVID-related mortality in the highest risk groups as a multiple of the COVID-related mortality in the non-highest risk population by date of death.



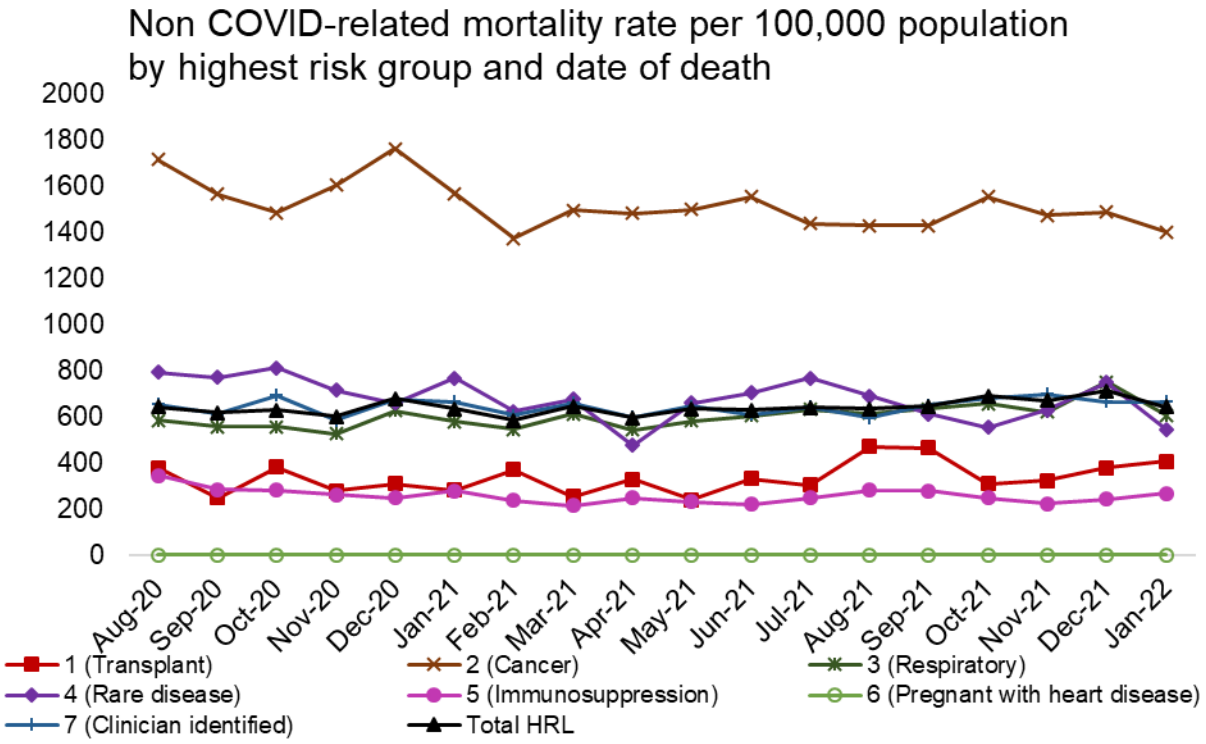
16.3 In January 2022, the cancer, clinician identified, and rare diseases groups had the highest COVID-related mortality rate(figure 10). There has been an increase in COVID-related mortality rates in most groups since December 2021(figure 10). As mentioned above, there have been no deaths in the pregnant with heart disease group.

Figure 8 - COVID-related mortality rate per 100,000 population by highest risk group and date of death.



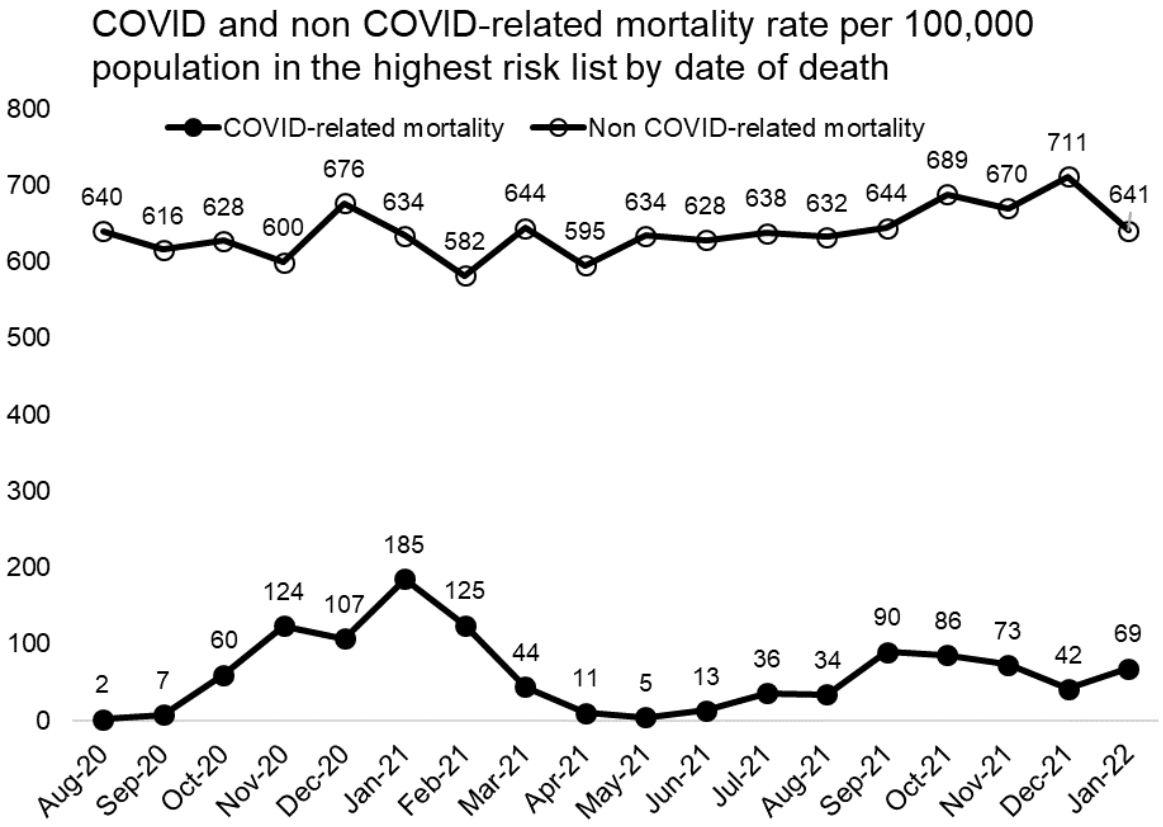
16.4 In comparison, the non COVID-related mortality rates in the Highest Risk List are more diverse, being the highest for the cancer group and lowest for the immunosuppression, transplant and pregnant with heart disease groups (figure 11).

Figure 9 - Non COVID-related mortality rate per 100,000 population by highest risk group and date of death.



16.5 Non COVID-related mortality is much higher than the COVID-related mortality (figure 12), for the Highest Risk List as a whole as well as for each individual group.

Figure 10 - COVID and non COVID-related mortality rate per 100,000 population in the highest risk list by date of death.



Annex C - Removal of groups from the Highest Risk List

The majority of those previously identified as highest risk do not face the same level of risk of severe illness or death from COVID-19 following the vaccination roll out and introduction of therapeutic treatments. This is reflected in the following conclusion and summary information:

17. Children

17.1 In Winter 2021, the NHS England Children and Young People National Clinical Director was commissioned by the Department of Health and Social Care to undertake an evidence review, to understand which children and young people are at highest risk from COVID-19 based on data and clinical intelligence[13].

17.2 On 15 July 2021, the 4 Chief Medical Officers reviewed evidence presented by the UK Government on risk to children and young people from COVID-19. They decided that all children and young people under 16 should be removed from the Highest Risk List, on the basis of extremely low rates of serious disease or mortality in this age group.

17.3 The evidence shows that a small number of children could still be advised by their GP or hospital clinician to follow stricter precautionary measures, as they would have been pre-pandemic, but there would no longer be any central shielding advice for children and young people, and they should be removed from the Shielding List.

17.4 The decision to remove children and young people from the List in Scotland was delayed as a precautionary measure, due to increases in the prevalence of the virus among younger age groups, and the severity of Delta at the time we proposed to remove them.

17.5 On 22 December 2022 the Joint Committee of Vaccination and Immunisation (JCVI) advised of primary vaccination of 5 to 11 year olds in a clinical risk group, which provides a further layer of protection[14] and supports the recommendation to remove children and young people from the Highest Risk List in Scotland. In a clinical trial, vaccine efficacy against COVID-19 in 5 to 11 year olds was 90.7%[15].

17.6 Booster vaccinations are also being offered to children and young people aged 12-15 who are in a clinical risk group, and those who are severely immunosuppressed and who have had a third primary dose.

17.7 As at 21 February 2022, there were 1,384 people under 16 on the Highest Risk List in Scotland, making up less than 1% of the overall list.

---

[13] Which children and young people are at higher risk of severe disease and death after SARS-CoV-2 infection: a systematic review and individual patient meta-analysis (medrxiv.org)
[14] JCVI statement on COVID-19 vaccination of children and young people: 22 December 2021 - GOV.UK (www.gov.uk)
[15] COVID-19: Pfizer vaccine provides 90% protection against infection in children aged 5-11, study finds | The BMJ

18. Group 1 – Solid organ transplant recipients

18.1 These are people who have had a transplant of the kidney, liver, pancreas, islet cell, heart, lung, stomach or other part of the intestine who are considered to be at higher risk due to the immunosuppression medication these individuals are required to take to stop rejection of transplanted organs.

18.2 A statement from NHS Blood and Transplant recommended vaccination as the best protection from severe disease, risk of hospitalisation and death from COVID-19.[16]

18.3 Data from Public Health Scotland showed that in January 2022 the transplant group had a COVID-related mortality rate 9 times higher than that of the non-highest risk population. This fell from a high of 59 times higher in June 2021.

18.4 The REACT-Scot study[17] recommended an option of passive immunisation therapies for solid organ transplant recipients for prevention in "those who have a medical condition making them unlikely to respond to or be protected by vaccination".

18.5 The COVID-19 Statistical Report[18] published in March 2022 by Public Health Scotland showed a decrease in the percentage of COVID-related deaths following a positive test in the transplant group from 17% in January 2021 to 2% in January 2022.

18.6 We will continue to review vaccine efficacy evidence and consider what future support would benefit this group of people.

18.7 As at 21 February 2022, there were 6,666 people within the transplant group on the HRL in Scotland, making up 4% of the overall list.

19. Group 2 – People with specific cancers

19.1 You are in this group if you:

- have cancer and are undergoing active chemotherapy, or have had radical radiotherapy for lung cancer
- have cancer of the blood or bone marrow and are at any stage of treatment. This includes cancers such as leukaemia, lymphoma or myeloma
- have cancer and are having immunotherapy or other continuing antibody treatments
- have cancer and are having specialised treatments that can affect the immune system. This includes protein kinase inhibitors or PARP inhibitors
- have had a bone marrow or stem cell transplant in the last 6 months, or if you are still taking immunosuppression drugs

[16] Latest NHS advice on COVID-19 vaccine for patients and recipients - NHS Organ Donation
[17] Efficacy of two doses of COVID-19 vaccine against severe COVID-19 in those with risk conditions and residual risk to the clinically extremely vulnerable: the REACT-SCOT case-control study | medRxiv
[18] COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

19.2 The cancer group had a COVID-related mortality rate 12 times higher than that of the non-highest risk population in January 2022. This group had the highest relative COVID-related mortality rate in January 2022, the same as the rare diseases and clinician identified groups (Figure 9).

19.3 The COVID-19 Statistical Report[19] published in March 2022 by Public Health Scotland showed a decrease in the percentage of COVID-related deaths following a positive test in the cancer group from 19% in January 2021 to 3% in January 2022.

19.4 We will continue to review vaccine efficacy evidence and consider what future support would benefit this group of people.

19.5 As at 21 February 2022, there were 25,630 people within the cancer group on the HRL in Scotland, making up 14% of the overall list.

20. Group 3 – People with severe respiratory conditions

20.1 You are in this group if you have:

- cystic fibrosis
- lung conditions which require home oxygen
- severe asthma requiring regular inhaler use and long-term steroid tablets to control your asthma – for example, Prednisolone or regular injections
- severe non-cystic fibrosis bronchiectasis
- pulmonary hypertension
- severe COPD. This usually means being on several different inhaler medications in the last year. This must include two long acting preventers as well as a steroid inhaler, for example, Long Acting Beta Agonists and Long Acting Anti-Muscarinic Antagonists. Severe COPD means that:
    - you are too breathless to walk 100 yards;
    - you have 2 or more lung infections a year, or;
    - you require oxygen to help with your breathing

20.2 The respiratory group had a COVID-related mortality rate 9 times higher than that of the non-highest risk population in January 2022. This was similar to those in the transplant group (Figure 9).

20.3 The number of COVID-related deaths remains highest for those in the respiratory and clinician identified groups in January 2022.

20.4 The COVID-19 Statistical Report published in March 2022 by Public Health Scotland showed a decrease in the percentage of COVID-related deaths following a positive test in the respiratory group from 23% in January 2021 to 1% in January 2022.

20.5 As at 21 February 2022, there were 70,049 people within the respiratory group on the HRL in Scotland, making up 39% of the overall list.

[19] COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

21. Group 4 – People with rare diseases

21.1 You are in this group if you have:

- An inborn error of metabolism which increases your risk of infection. Examples include Severe Combined Immunodeficiency (SCID) and homozygous sickle cell disease
- Interstitial Lung Disease (ILD)
- Sarcoidosis
- Down's syndrome, and you are aged 18 or over

There are many conditions classed as a rare disease but not everyone with a rare disease would be considered to be at a higher risk of COVID-19.

21.2 The rare diseases group had generally low relative mortality rates ranging from 0 to 9 times higher than that of the non-highest risk population between April and August 2021, however there was an increase in September 2021 to a relative mortality rate of 20 times higher. This reduced to a mortality rate of 12 times higher than that of the non-highest risk population in January 2022 (Figure 9).

21.3 This group had the highest relative COVID-related mortality rate in January 2022, same as the cancer and clinician identified groups. (Figure 9).

21.4 The COVID-19 Statistical Report[20] published in March 2022 by Public Health Scotland showed a decrease in the percentage of COVID-related deaths following a positive test in the rare diseases group from 25% in January 2021 to 2% in January 2022.

21.5 As at 21 February 2022, there were 10,647 people within the rare diseases group on the HRL in Scotland, making up 6% of the overall list.

22. Group 5 – People on immunosuppression therapies which increase risk of infection

22.1 These are people who:

- may also belong to other groups, for example, because they are on immunosuppressive therapy for organ transplants
- may be on a high dose of corticosteroids (equal to Prednisolone 20 mg or more per day) for more than 4 weeks, or on a lower dose of corticosteroids for more than 4 weeks, combined with other disease modifying medications
- are on specific single therapies, for example Cyclophosphamide (usually prescribed by hospital specialists), and those on disease modifying medications who also have other chronic medical conditions

22.2 The immunosuppressed group had a COVID-related mortality rate 6 times higher than that of the non-highest risk population in January 2022 (Figure 9).

[20] COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

22.3 In August 2021 initial data published from the OCTAVE study[21] into vaccine responses in patients with impaired immune systems found the following:

- For the majority the immune response to the COVID-19 vaccine was equitable to that of someone with a full immune system
- 40% mounted a low response following two doses of the vaccine
- 11% failed to generate any antibodies four weeks after two doses of the vaccine

22.4 This study contributed as significant evidence supporting a third dose of vaccine to those who are severely immunosuppressed.

22.5 In September 2021 the JCVI defined the criteria for severe immunosuppression[22] and recommended a third primary dose be offered to individuals aged 12 years and over who were severely immunosuppressed around the time of their first or second COVID-19 vaccine.

22.6 As at 10 March 2022, 91% of those identified for a third COVID-19 vaccination dose because they are severely immunosuppressed have received it.

22.7 It's important to note individuals within this group who have conditions that reduce their vaccine response, or who take medication that has a similar effect, have always been at risk of infectious disease, and continue to take precautionary measures based on their individual circumstance and the advice of their own GP and clinician, just as they would have prior to COVID. However, those who are newly diagnosed may not have previous experience of taking precautionary measures.

22.8 Consideration should be given to findings from the Octave study, which advised the level of antibodies required for protection from COVID-19 is still not known. These findings therefore do not provide a conclusive assessment of the protection vaccines offer people with weakened immune systems.

22.9 The COVID-19 Statistical Report[23] published in March 2022 by Public Health Scotland showed a decrease in the percentage of COVID-related deaths following a positive test in the immunosuppression group from 12% in January 2021 to 1% in January 2022.

22.10 We will continue to review vaccine efficacy evidence and consider what future support would benefit this group of people.

22.11 As at 21 February 2022, there were 36,268 people within the immunosuppressed group on the HRL in Scotland, making up 20% of the overall list.

---

[21] The OCTAVE Study

[22] Joint Committee on Vaccination and Immunisation (JCVI) advice on third primary dose vaccination - GOV.UK (www.gov.uk)

[23] COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

23. Group 6 – People who are pregnant and have significant heart disease.

23.1 There have been no COVID-related deaths in this group at any point throughout the pandemic.

23.2 There was initially much reluctance among people who were pregnant to receive vaccinations because of mixed reports of side-effects, however clinicians and advisers are clear it is safe to get the vaccine if you are pregnant. This was confirmed in the Royal College of Obstetricians and Gynaecologist's Coronavirus (COVID-19) Infections in Pregnancy report[24], published March 2022.

23.3 There is a lack of research specifically into this particular highest risk category.

23.4 Finally, this is a small group and data is not published due to the sample size, but for the reasons outlined there is a strong argument that this group could be deemed as no longer considered highest risk.

24. Group 7 – Clinical judgement, people receiving renal dialysis treatment, people with chronic kidney disease stage 5, people who have liver cirrhosis (Child-Pugh Class B and C) and people who have had their spleen removed

24.1 These are people who have been identified by their clinician or patient groups who were considered to be at highest risk after the original shielding criteria was defined.

24.2 The clinician identified group had a COVID-related mortality rate 12 times higher than that of the non-highest risk population in January 2022 (Figure 9).

24.3 This group had the highest relative COVID-related mortality rate in January 2022, same as the cancer and rare diseases groups. (Figure 9)

24.4 Due to the range of conditions within this group, little research has been carried out on this specific group.

24.5 The COVID-19 Statistical Report[25] published in March 2022 by Public Health Scotland showed a decrease in the percentage of COVID-related deaths following a positive test in the clinician identified group from 21% in January 2021 to 2% in January 2022.

24.6 As at 21 February 2022, there were 50,778 people within the clinician identified group on the HRL in Scotland, making up 29% of the overall list.

[24] Coronavirus (COVID-19), infection in pregnancy | RCOG
[25] COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

Annex D - Summary of Work to understand people on the Highest Risk List

The following section provides an at a glance summary of the main high level findings of this review, and may assist GP or Clinician discussions about risk with individual patients and the people they support. The findings are presented in charts representing each Highest Risk List grouping, with an additional chart for Children and Young People on the Highest Risk List.

Children	Output
High level findings from mortality data	• COVID-related deaths for those on the highest risk list are recorded by Highest Risk List groups therefore specific data on children is not available.
High level findings from risk of serious disease	• Children & young people were at very low risk of severe illness and death from COVID-19.
High level findings from meta-analysis	• The mortality rate of children & young people who died from SARS-CoV -2 in England equates to 2 per million between Mar 2020 and Feb 2021.
High level vaccination rates	• Vaccination rates in 12 to 15 year olds at higher risk of COVID-19 in Jul 2021 showed: 75.8% received Dose 1 57.7% received Dose 2
Useful Research Links:	Public Health Scotland COVID-19 Statistical Report JCVI statement on COVID-19 vaccination of children and young people: 22 December 2021 - GOV.UK (www.gov.uk) COVID-19: Pfizer vaccine provides 90% protection against infection in children aged 5-11, study finds | The BMJ Efficacy of two doses of COVID-19 vaccine against severe COVID-19 in those with risk conditions and residual risk to the clinically extremely vulnerable: the REACT-SCOT case-control study.

Transplant	Output
High level findings from mortality data	• 110 COVID-related deaths following a positive test in the transplant group between August 2020 and January 2022. • The number of COVID-related deaths following a positive test was the lowest in the transplant group between August 2020 and January 2022. There has also been a decrease in the number of COVID-related deaths following a positive test in this group from 15 in January 2021 to 7 in January 2022.
High level findings from risk of serious disease	• Strong recommendation that, wherever possible, transplant recipients and patients on the transplant waiting list should have two doses of the vaccine for maximum protection against contracting or dying from COVID-19.

	• REACT-SCOT study found: In comparison with double-vaccinated individuals of the same age and sex without risk conditions, double-vaccinated solid organ transplant recipients have a rate ratio of the order of 100-fold for severe disease, but even in this group the absolute risk of severe disease in the double-vaccinated is less than 1 in 1000 per month.
High level findings from meta-analysis	• Third dose of vaccine does bring significant amplification of immune response. • In January 2022 the transplant group had a COVID-related mortality rate 9 times higher than that of the non-highest risk population. This fell from a high of 59 times higher in June 2021.
High level vaccination rates	• Vaccination rates in people who were advised to shield as of Jan 2022 are; 97% Dose 1 96% Dose 2 91% Booster or Dose 3 *no further breakdown of rates in specific highest risk groups is available.
Useful Research Links:	Public Health Scotland COVID-19 Statistical Report Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients | NEJM 'Immunological responses to SARS-CoV-2 vaccines in kidney transplant recipients'. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. Efficacy of two doses of COVID-19 vaccine against severe COVID-19 in those with risk conditions and residual risk to the clinically extremely vulnerable: the REACT-SCOT case-control study COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

Specific Cancers	Output
High level findings from mortality data	• 364 COVID-related deaths following a positive test in the cancer group between August 2020 and January 2022. • Decrease in COVID-related deaths following a positive test in this group, from 63 in January 2021 to 28 in January 2022.
High level findings from risk of serious disease	• Two doses of vaccine protect against severe COVID-19 in CEV individuals but the residual risk in

	double-vaccinated individuals remains far higher in those who are CEV than in those who are not.
High level findings from meta-analysis	• The cancer group had a COVID-related mortality rate 12 times higher than that of the non-highest risk population in January 2022. This group had the highest relative COVID-related mortality rate in January 2022, the same as the rare diseases and clinician identified groups.
High level vaccination rates	• Vaccination rates in people who were advised to shield as of Jan 2022 are; 97% Dose 1 96% Dose 2 91% Booster or Dose 3 *no further breakdown of rates in specific highest risk groups is available.
Useful Research Links:	Efficacy of two doses of COVID-19 vaccine against severe COVID-19 in those with risk conditions and residual risk to the clinically extremely vulnerable: the REACT-SCOT case-control study COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

Respiratory	Output
High level findings from mortality data	• 919 COVID-related deaths following a positive test in the respiratory group between August 2020 and January 2022. • The number of COVID-19 related deaths following a positive test was the highest for those in the respiratory group between August 2020 and January 2022. Although there has been a decrease in the number of COVID-related deaths following a positive test from 205 in January 2021 to 32 in January 2022.
High level findings from risk of serious disease	• Two doses of vaccine protect against severe COVID-19 in CEV individuals but the residual risk in double-vaccinated individuals remains far higher in those who are CEV than in those who are not.
High level findings from meta-analysis	• The respiratory group had a COVID-related mortality rate 9 times higher than that of the non-highest risk population in January 2022. This was similar to those in the transplant group.
High level vaccination rates	• Vaccination rates in people who were advised to shield as of Jan 2022 are; 97% Dose 1 96% Dose 2 91% Booster or Dose 3

	*no further breakdown of rates in specific highest risk groups is available.
Useful Research Links:	Public Health Scotland COVID-19 Statistical Report Efficacy of two doses of COVID-19 vaccine against severe COVID-19 in those with risk conditions and residual risk to the clinically extremely vulnerable: the REACT-SCOT case-control study COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

Rare Diseases	Output
High level findings from mortality data	• 170 COVID-related deaths following a positive test in the rare diseases group between August 2020 and January 2022. • There has been a decrease in the number of COVID-related deaths following a positive test in this group from 34 in January 2021 to 8 in January 2022. Among the lower groups within the HRL.
High level findings from risk of serious disease	• The number of COVID-related deaths following a positive test was the second lowest in the rare diseases group between August 2020 and January 2022.
High level findings from meta-analysis	• The rare diseases group had generally low relative mortality rates ranging from 0 to 9 times higher than that of the non-highest risk population between April and August 2021, however there was an increase in September 2021 to a relative mortality rate of 20 times higher. This reduced to a mortality rate of 12 times higher than that of the non-highest risk population in January 2022.
High level vaccination rates	• Vaccination rates in people who were advised to shield as of Jan 2022 are; 97% Dose 1 96% Dose 2 91% Booster or Dose 3 *no further breakdown of rates in specific highest risk groups is available.
Useful Research Links:	Public Health Scotland COVID-19 Statistical Report Efficacy of two doses of COVID-19 vaccine against severe COVID-19 in those with risk conditions and residual risk to the clinically extremely vulnerable: the REACT-SCOT case-control study COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

Immunosuppressed	Output
High level findings from mortality data	• 306 COVID-related deaths following a positive test in the immunosuppression group between August 2020 and January 2022. • There has been a decrease in the number of COVID-related deaths following a positive test in this group from 44 in January 2021 to 15 in January 2022.
High level findings from risk of serious disease	• The OCTAVE trial has published preliminary data today showing that 89% of people who are immunocompromised or immunosuppressed generate antibodies following vaccination, and 60% generated a strong antibody response following 2 doses of a vaccine. • However, 40% of people in these groups mounted a low, or undetectable, immune response after 2 doses, and the level of antibody response varies between the groups studied. • The level of antibodies required for protection from COVID-19 is still not known. These findings therefore do not provide a conclusive assessment of the protection vaccines offer people with weakened immune systems.
High level findings from meta-analysis	• For the majority the immune response to the COVID-19 vaccine was equitable to that of someone with a full immune system. • 40% of people in the patient groups mounted a low response following two doses of the vaccine. • 11% of immunocompromised patients failed to generate any antibodies four weeks after two doses of the vaccine.
High level vaccination rates	• Vaccination rates in people who are severely Immunosuppressed as of 05 April 2022 were; 97% Dose 1 96% Dose 2 92% Booster or Dose 3 56% Dose 4
Useful Research Links:	Public Health Scotland COVID-19 Statistical Report Joint Committee on Vaccination and Immunisation (JCVI) advice on third primary dose vaccination - GOV.UK (www.gov.uk) . Examining the immunological effects of COVID-19 vaccination in patients with conditions potentially leading to diminished immune response capacity – the OCTAVE Trial.

	COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland
Pregnant Women with Heart Disease	Output
High level findings from mortality data	• Zero COVID-related deaths in the pregnant with heart disease group..
High level findings from risk of serious disease	• There were no COVID-related deaths in this group.
High level findings from meta-analysis	• No research available specifically regarding pregnant women with heart disease. • Recent publication of Coronavirus (COVID-19) Infection in Pregnancy review by Royal College of Midwives and Royal college of Obstetricians & gynaecologists found; 1)"Pregnant women do not appear more likely to contract COVID-19 than the general population." 2)"Pregnant women who have had 2 doses and a booster (or three doses) of vaccine are 88% less likely to be admitted to hospital with the omicron variant than those who have not been vaccinated."
High level vaccination rates	• Vaccination rates in people who were advised to shield as of Jan 2022 are; 97% Dose 1 96% Dose 2 91% Booster or Dose 3 *no further breakdown of rates in specific highest risk groups is available.
Useful Research Links:	Public Health Scotland COVID-19 Statistical Report Coronavirus (COVID-19), infection in pregnancy | RCOG COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

Clinician Identified	Output
High level findings from mortality data	• 690 COVID-related deaths following a positive test in the clinician identified group between August 2020 and January 2022. • There has been a decrease in number of COVID-related deaths following a positive test in this group from 146 in January 2021 to 43 in January 2022. The number of COVID-related deaths following a positive test was the second highest in the clinician identified group between August 2020 and January 2022.
High level findings from risk of serious disease	• Two doses of vaccine protect against severe COVID-19 in CEV individuals but the residual risk in

	double-vaccinated individuals remains far higher in those who are CEV than in those who are not.
High level findings from meta-analysis	• The clinician identified group had a COVID-related mortality rate 12 times higher than that of the non-highest risk population in January 2022. This group had the highest relative COVID-related mortality rate in January 2022, same as the cancer and rare diseases groups.
High level vaccination rates	• Vaccination rates in people who were advised to shield as of Jan 2022 are; 97% Dose 1 96% Dose 2 91% Booster or Dose 3 *no further breakdown of rates in specific highest risk groups is available.
Useful Research Links:	Public Health Scotland COVID-19 Statistical Report Efficacy of two doses of COVID-19 vaccine against severe COVID-19 in those with risk conditions and residual risk to the clinically extremely vulnerable: the REACT-SCOT case-control study | medRxiv COVID-19 statistical report - 2 March 2022 - COVID-19 statistical report - Publications - Public Health Scotland

This publication is available at **www.gov.scot**

Any enquiries regarding this publication should be sent to us at

The Scottish Government
St Andrew's House
Edinburgh
EH1 3DG

ISBN: 978-1-80201-731-1 (web only)

Published by The Scottish Government, April 2022

Produced for The Scottish Government by APS Group Scotland, 21 Tennant Street, Edinburgh EH6 5NA
PPDAS1099582 (05/22)