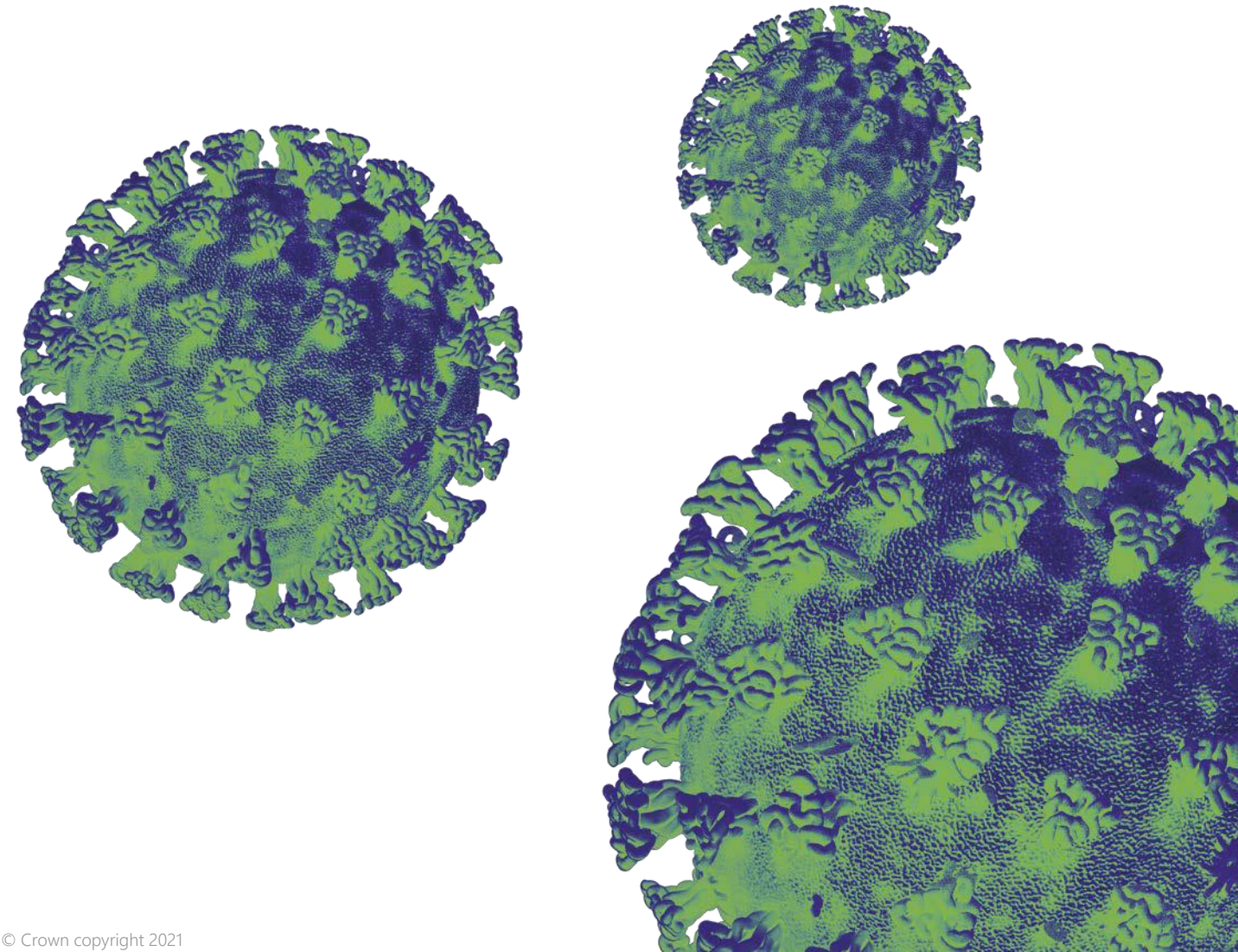
Llywodraeth Cymru
Welsh Government

Y Gell Cyngor Technegol

Crynodeb o'r Cyngor

10 Rhagfyr 2021



Y Gell Cyngor Technegol: Briff Mewnol

10 Rhagfyr 2021

Datganiad agoriadol - Omicron

- Mae'r amrywiolyn Omicron wedi peri pryder sylweddol o ganlyniad i'r dystiolaeth gynyddol o ddihangiad imiwnyddol uwch a chyfradd twf llawer uwch na'r amrywiolyn Delta.
- Mae llawer o'r dystiolaeth sy'n dod i'r amlwg yn dal i fod yn y camau rhagarweiniol ac mae bylchau yn parhau i fod yn yr hyn rydym yn ei ddeall am effaith yr amrywiolyn ar yr ymateb imiwnyddol ehangach, effeithiolrwydd y brechlyn, trosglwyddadwyedd, difrifoldeb y salwch a darlun clir am gyffredinrwydd yr amrywiolyn yn rhyngwladol. Dylai mesurau i wella ymddygiadau amddiffynnol yn y boblogaeth arafu dyfodiad yr amrywiolyn i Gymru. Fodd bynnag, bydd hyn yn golygu y bydd rhaid i boblogaeth Cymru ddeall y mesurau a'r rhesymau dros eu rhoi ar waith, a'u defnyddio yn eang. Bydd rhaid hefyd eu gorfodi yn gyson. Os yw Omicron neu Delta yn tyfu ar yr un raddfa a welwyd mewn gwledydd cymharol yn rhyngwladol, bydd angen mesurau mwy caeth.
- Mae'r gwaith modelu rhagarweiniol gan y Grŵp Cynghori Gwyddonol ar Argyfyngau (SAGE) yn awgrymu, heb wneud unrhyw newidiadau i'r mesurau sydd ar waith, y gall nifer y bobl sydd yn yr ysbyty gyda Omicron gyrraedd 1,000 y dydd neu fwy yn Lloegr erbyn diwedd y flwyddyn, gan gynyddu i lefelau uwch na'r brigiadau blaenorol yn 2022.
- Mae'r dystiolaeth yn gyffredinol yn awgrymu bod Omicron yn tyfu'n llawer cyflymach na'r amrywiolyn Delta. I'r rhai hynny sy'n manteisio ar y pigiad atgyfnerthu, dylai'r amddiffyniad rhag Omicron fod yn debyg i'r hyn a welwyd gyda Delta am sawl mis. Effaith uniongyrchol fwyaf Omicron yw'r gyfradd twf eithriadol o uchel a'r posibilrwydd y bydd nifer uchel o achosion. Hyd yn oed os yw cyfran yr achosion difrifol yn fach, gallai'r niferoedd cyffredinol fod yn sylweddol.
- Mae nifer yr heintiau Omicron yn y DU eisoes yn cynyddu'n gyflym, gyda thystiolaeth o drosglwyddiad cymunedol ac amser dyblu o 3 diwrnod. Er ei bod yn ansicr iawn pa gyfradd o'r achosion a fydd yn cael eu derbyn i'r ysbyty yn y pen draw, disgwylir i bobl ddechrau cael eu derbyn i'r ysbyty'n fuan. Nes bydd y rhaglen brechlynnau atgyfnerthu wedi'i chwblhau, bydd y risg o darfu a'r risg o niwed i iechyd, i'r gymdeithas ac i'r economi os bydd nifer yr achosion yn cynyddu'n gyflym yn sylweddol.

Crynodeb o'r prif bwyntiau

Crynodeb o sefyllfa Cymru

- Yn gyffredinol mae'r achosion o COVID-19 wedi aros yn sefydlog ar draws Cymru dros y pythefnos diwethaf, sef oddeutu 500 o achosion am bob 100,000 o bobl, ac mae positifedd profion wedi lleihau'n raddol i ychydig o dan 17%. Cynyddodd achosion cymaint â 2.11% yn y cyfnod 7 diwrnod hyd 27 Tachwedd i 469.86 o achosion am bob 100,000 o bobl.

- Yn ôl y Swyddfa Ystadegau Gwladol, ar gyfer yr wythnos 25 Tachwedd i 1 Rhagfyr, amcangyfrifir fod gan 1.98% o bobl yng Nghymru COVID-19. Mae hyn gyfwerth ag oddeutu 1 person ym mhob 50, neu 60,300 o bobl yn ystod y cyfnod hwn.
- Mae nifer y gwelyau a ddefnyddir gan gleifion COVID-19 wedi lleihau'n ddiweddar. Fodd bynnag, rhwng dechrau mis Gorffennaf 2021 a dechrau mis Tachwedd 2021, cynyddodd y pwysau o ganlyniad i COVID-19 ar y GIG yn gyffredinol.
- Mae cyfanswm y marwolaethau wythnosol o ganlyniad i COVID-19 wedi lleihau'n raddol yn ystod mis Tachwedd; yn ystod y cyfnod 7 diwrnod diweddaraf hyd 27 Tachwedd, fe wnaeth y marwolaethau wythnosol leihau o 54 i 39, yn ôl Iechyd Cyhoeddus Cymru, ac mae nifer y marwolaethau'n parhau'n gymharol isel o'i gymharu â chyfnodau blaenorol pan oedd nifer yr achosion yn debyg.
- Mae amcangyfrif consensws UKHSA o'r rhif atgynhyrchu ar gyfer Cymru rhwng 0.9 a 1.1 ac amser haneru o rhwng -29 diwrnod (ac yn lleihau) a gwerth gwastad, tra bod amcangyfrif Iechyd Cyhoeddus Cymru yn 1.05 gydag amser dyblu o 57.5 diwrnod. Noder bod oedi o tua 2-3 wythnos fel arfer yn amcangyfrif y Gyd-ganolfan Bioddiogelwch a bod oedi o tua wythnos yn amcangyfrif Iechyd Cyhoeddus Cymru, sy'n defnyddio methodoleg wahanol.
- Mae lledaeniad RSV mewn plant o dan 5 oed wedi lleihau i lefelau isel ac nid yw'r ffliw yn lledaenu yng Nghymru ar hyn o bryd, gyda llai o achosion tymhorol na'r llinell sylfaen.

SAGE 98 summary

- Evidence from SAGE as at 7 December suggests the number of Omicron infections in the UK is increasing rapidly with a doubling time of 3-5 days (high confidence).There is evidence of community transmission, and hospital admissions from Omicron should be expected to follow soon (high confidence).
    - Several other sources of data from the UK show evidence of Omicron having a growth advantage over Delta, including household studies which show higher secondary attack rates (high confidence), although the underlying mechanisms are unclear and both increased transmissibility and escape from immunity are likely to play a role.
    - Some early indications from South Africa suggest less severe disease in those hospitalised when compared to previous waves, though this likely reflects at least in part the characteristics of those being admitted to date, who are younger than in previous waves (low confidence). A modest reduction in severity would not avert high numbers of hospitalisations if growth rates remained very high.
    - Preliminary modelling suggests that without any changes to measures in place, the number of hospitalisations from Omicron may reach 1,000 per day or higher in England by the end of the year (and still be increasing at that point). The overall scale of any wave of hospitalisations without interventions is highly uncertain, but the peak could reach several times this level. The peak is highly likely to be higher than 1,000 to 2,000 Omicron hospital admissions per day without intervention to slow the speed of increasing infections.

- There are other impacts from high levels of incidence aside from hospitalisations and deaths, including the morbidity burden in those who are not hospitalised and workforce absences. With very rapid doubling times a large wave could occur leading to synchronous absences from work.
- It is highly likely that Omicron will account for the majority of new SARS-CoV-2 infections in the UK within a few weeks. Given the rapid increase, decision makers will need to consider urgently which measures to introduce to slow the growth of infections if the aim is to reduce the likelihood of unsustainable pressure on the NHS. The faster the growth in infections at the point measures are introduced, the more admissions will increase in the period between action being taken and the number of admissions being affected. With lags of the order of two or more weeks, and doubling times of the order of three days, it is likely that, once hospitalisations begin to increase at a rate similar to that of cases, four doublings (i.e. a 16-fold increase) or more could already be "in the system" before interventions that slow infections are reflected in hospitalisations.
- Taking measures which slow or delay the wave of infections would allow more time for vaccination including ensuring increased coverage and boosting with existing vaccines. Laboratory neutralisation data will give an early indication of vaccine protection against Omicron infection over the next week, although data on infections and hospitalisations will be needed
- The effectiveness of these will be dependent on the measures chosen, and also on behavioural responses. Evidence suggests that measures could be reintroduced with expectation of a similar level of adherence as has been seen in the past. Adherence is likely to be higher if messaging and policy have clear rationales and are consistent. Consistency across the UK may help with messaging.

- A SPI-M consensus statement from 1 December suggests that increase immune escape and/or transmissibility in the Delta variant will likely necessitate very stringent measures in order to control growth and keep R below 1. Delaying any wave of infections in such a scenario would allow more time for vaccinations and therapeutics to be modified to combat omicron.
- A NERVTAG paper on antiviral drug resistance highlights that Omicron may remove some possible combination therapy options which could increase the risk of resistance to monoclonal antibodies. Antiviral dosing and duration should consider the need to minimise the risk of resistance. These are the same principles used for other antimicrobial therapies. It may be appropriate to provide monitoring and support of adherence.

COVID-19 evidence summary

Omicron

- The UKHSA has published its variant risk assessment for Omicron. A Red RAG status has been assigned to the variant's increased growth advantage, evasion of Infection and vaccine acquired immunity (moderate to high confidence), while impact of the variant on transmissibility has been given amber status (low confidence). In the initial risk assessment therapeutics was also given a red status with low confidence as a result of mutations suggestive of reduced therapeutic effectiveness

- The UKHSA's more detailed variant technical briefing highlights that Omicron cases appear to be rising fastest in London, followed by East Midlands and South East England. Of the 22 confirmed cases, the age/sex distribution shows Omicron mainly affecting young & middle-aged adults. Only 1 case is in a child and 0 cases are in people aged 70+. 8/17 cases have known travel to a Red List country while 7/17 have unknown travel status (to date). There have been no hospitalisations or deaths in these cases. **Note: a subsequent variant technical briefing has been published since this report was drafted and is available here.**

- Several different neutralisation studies containing experimental data have been made public this week, all confirming that antibody neutralisation against Omicron infection from vaccines or natural infection is reduced to a greater extent than any previous variant of concern. Although there remains uncertainty at this stage, overall there is strong indication protection against infection is severely reduced for two doses of vaccine, **although there is a consistent message that boosters provide a level of antibody immunity required to neutralise the virus**. More laboratory data and accompanying analysis will continue to emerge, along with real-world vaccine effectiveness data.

- There have been media reports of Omicron-related super-spreader events in a number of countries- global monitoring of this variant to increase understanding of this variant will continue in coming weeks.

- The ECDC have updated their Omicron threat assessment- although robust evidence is still limited there is much alignment with the UKHSA assessment. The ECDC urges countries to give priority towards unvaccinated priority groups and boosters for those aged 40 and older, followed by younger age groups. Non-pharmaceutical interventions should continue to be implemented in countries and enhanced contact tracing and genomic surveillance remain critical for the early detection and response to the Omicron variant.

- The first study of reinfection from the Omicron variant in South Africa suggests a risk of reinfection 2.39 times greater than the Delta variant, which will have significant implications for informing the public health response. It should be noted that these results are not directly comparable with more vaccinated countries like the UK and more data will be needed before the global impact of Omicron can be understood.

Vaccines

- The study which informed the JCVI advice on booster vaccination, COV-BOOST, has been published. The trial demonstrated the potential of vaccines tested to boost immunity following an initial course of two doses of AstraZeneca or Pfizer with similar results between age groups and no safety concerns identified. The mRNA vaccines shoed increased antibody responses after two doses of AstraZeneca or

Pfizer; however AztraZeneca did not boost cellular responses after two doses of AstraZeneca.

- A study from Israel of around 300,000 adults aged 40+ suggests those who received a third booster dose of the Pfizer vaccine saw an 86% reduction in the odds of infection within a few weeks. The analysis also suggest that individuals who received the booster dose have a lower odds of hospitalization than those receiving 2 doses, although there were some potential confounders. More long-term study will be required to understand the duration of immunity following a booster dose.

- An online survey study investigating expectations of vaccine side-effects in 1,470 unvaccinated adults in the UK highlights the importance of transparent and accurate communication about the likelihood and nature of side effects from vaccination. Messaging should emphasise the safety, effectiveness, and widespread uptake of vaccination, while promoting accurate perceptions of the incidence of vaccination side effects and providing reassurance about the typically transitory and non-harmful nature of these side-effects.

Inequalities and indirect harms

- The UK Government has published its report on progress to address COVID-19 health inequalities. The report includes a summary of progress against recommendations from previous reports, lessons learnt from this work and an action plan for addressing some of the longer-term issues identified during the course of this project. The report also includes further analysis of how the impacts of COVID-19 changed for ethnic minority groups between the first and second waves of the pandemic.

Treatments

- A second monoclonal antibody treatment (nMAB), Sotrovimab, has been approved by the MHRA after it was found to be safe and effective at reducing the risk of hospitalisation and death in people with mild to moderate COVID-19 infection who are at an increased risk of developing severe disease. In a clinical trial, a single dose of the monoclonal antibody was found to reduce the risk of hospitalisation and death by 79% in high-risk adults with symptomatic COVID-19 infection.

- The previous nMAB, Ronapreve has been available for patients hospitalised with COVID since September 2021. Later this month access to Ronapreve will be extended to non-hospitalised patients who are considered to be at highest risk of progression to severe disease, hospital admission or death.

Education and Children

- A rapid evidence review of measures to support safe return to university campuses supports six measures: encouraging vaccination, wearing face coverings, physical distancing, improving ventilation, test and isolating students and staff and supporting vulnerable people to work remotely. These should be combined into a multi-faceted strategy to maximise student safety and ensure continuation of education provision.

- A Wales COVID-19 Evidence Centre (WCEC) rapid review of the impact of COVID-19 educational restrictions on children aged 3-13 highlights that further research is

required, although there was a recommendation to strengthen the home learning environment for more vulnerable learners was.

Epidemiology and Clinical

- A study of infection rates for Welsh care home residents following vaccination using the data in the SAIL databank up to March 2021 suggests most infections post-vaccination occurred within 28 days of receiving their vaccine, suggesting extra vigilance and precautions to reduce transmission risk for this highly vulnerable population should be taken in this time frame. Overall increased risk of infection after 21 days was also associated with frailty, which saw up to an almost 5-fold increase.
- A WCEC review highlights a number of Long COVID studies currently operating or being set up in Wales.

Non-pharmaceutical interventions

- The UK Government has published the Phase II and III findings of its Event Research Programme, examining audiences return to mass events and the risk of transmission. The studies demonstrate that environmental and behavioural risk factors associated with COVID-19 transmission at events are complex and contextual. Risk is increased with prolonged and repeated exposure to poor air quality, insufficient ventilation, reduced distancing between individuals or limited compliance with face covering.
- Approximately 1.7% of attendees, for whom data were available, tested positive for COVID-19 during their 16 day study period. The results tend to show that there was little evidence of increased transmission by attendance at the following categories of events: mainly outdoor seated, mainly outdoor partially seated or the indoor seated theatre events studied. However, some events such as theatres were run at or below 50% of normal full capacity and involved low numbers of attendees, meaning the study was unable to rule out a potentially important increased risk of transmission.
- These pilot around the NHS app and certification found compliance with certification protocols improved with clearer and more consistent communications, which aided the avoidance of confusion. They demonstrated the importance of having properly trained stewards who are equipped to rapidly and accurately verify COVID status, in order to minimise queuing and associated safety and security concerns.
- An article in the BMJ examines three distinct international approaches to mitigating COVID-19- aggressive containment, suppression and mitigation. In general countries that opted for aggressive containment had lower deaths per million than those that took other approaches, although this may not be sustainable in the long term.
- Successful containment requires countries to take immediate action in response to emerging outbreaks and clearly define the targets for relaxing interventions. Success is also underpinned by trust in policy makers and government and community engagement and facilitated by strong political commitment, well prepared public health systems, and scientific input into policy making.

Wales Sit-Rep

- The latest fortnightly COVID-19 Situational Report, containing the most recent data on epidemiological surveillance, NHS status, wastewater monitoring, education and children, international travel, mobility, vaccination and population immunity and forward projections for Wales is available here. **Note the previous report will be updated next week.**
- Overall cases of COVID-19 have remained stable across Wales over the last two weeks, and test positivity has remained stable. Cases have risen by 2.11% in the 7 day period ending 27 November to 469.86 cases per 100,000. Test positivity during the same period has decreased but remains at a high level of 16.97%. We will need to continue monitoring case rates and other key indicators in each nation carefully to better understand the impact of easements of restrictions, return of schools and universities, and impact on the NHS.
- For the week 25 November to 1 December, it is estimated that 1.98% of the community population had COVID-19. This equates to approximately 1 person in every 50, or 60,300 people during this time.
- The number of beds occupied with COVID-19 related patients (confirmed, suspected and recovering) has recently decreased. However, from early July 2021 to early November 2021, COVID-19 pressure on the NHS generally increased. The number of COVID-19 related patients (confirmed, suspected and recovering) occupying a hospital bed has decreased to 449 in the week ending 26 November.
- There are 39 patients with suspected or confirmed COVID-19 in critical care beds in Wales. This is 125 lower than the maximum COVID-19 position of approximately 164. The total number of patients in critical care for both COVID-19 and non-COVID-19 stands at 187, 35 more than the 152 baseline number of critical care beds available before the COVID-19 pandemic.
- The total number of weekly COVID-19 deaths has decreased during the most recent 7-day period ending 27 November from 54 to 39 according to PHW and remains low in comparison to previous waves during periods of similar incidence.
- The UKHSA consensus estimate of the reproduction number for Wales is between 0.9 and 1.1 and a doubling time of -29 days to flat (as at 09 December 2021), while PHW's estimate is 1.05 with a doubling time of 57.5 days (as at 08 December 2021). Note that the UKHSA estimate is typically lagged by 2-3 weeks while PHW, which uses a different methodology, is lagged by around 1 week.
- As at 05 December 2021, a total of 5,386,809 doses of COVID-19 vaccine were given in Wales and recorded in the COVID-19 Welsh Immunisation System. 2,474,162 were first doses. 2,275,434 were second doses. 997,844 were booster doses. 43,700 were third dose primary course recommended for severely immunosuppressed individuals. *Source: PHW*.
- The most recent PHW weekly Influenza and Acute Respiratory Infection report dated 8 December suggests the number of confirmed cases of RSV in children aged under 5 years across Wales has continued to decrease and is now at low intensity levels. Influenza is still not currently circulating in Wales and remains far below the baseline seasonal threshold for seasonal influenza activity. Rhinovirus,

human metapneumovirus and adenovirus are the most commonly detected cause of non-COVID-19 Acute Respiratory Infection (ARI).

SAGE 98 7 December 2021

SAGE 98 Official Minutes

- The number of Omicron infections in the UK is now increasing rapidly, with evidence of community transmission, and hospital admissions from Omicron should be expected to follow soon (high confidence). Though there remain some important uncertainties, the emerging data from the UK is broadly consistent with early indications from South Africa. With the speed of growth seen, decision makers will need to consider response measures urgently to reduce transmission if the aim is to reduce the likelihood of unsustainable pressure on the NHS.
- The spread of Omicron in the UK appears to be following a similar trajectory to that seen in South Africa; though there are many differences between the UK and South Africa it will remain important to monitor the situation there. Early verbal reports indicate that hospitalisations due to Omicron are now increasing in South Africa.
- The number of new suspected daily Omicron cases identified is now in the hundreds (based on S-gene target failure (SGTF) data) and it is highly likely that the actual number of daily infections in the UK is in the thousands.
- The doubling time for new Omicron infections is currently around 3 days in England and although some potential biases in the data lead to some uncertainty around this growth rate, it is unlikely to be any slower than a 5-day doubling time (high confidence). Omicron cases are making up an increasing proportion of SGTF cases, which will allow this estimate to be refined.
- Several other sources of data from the UK also show evidence of Omicron having a growth advantage over Delta, including household studies which show higher secondary attack rates (high confidence).
- The underlying mechanisms of the growth rate advantage of Omicron remain unclear. Both increased transmissibility and escape from immunity (following infection and/or vaccination) are likely to play a role, although the relative contribution of each of these, or any other factors, is not yet known. Preliminary modelling suggests a similar number of infections and hospitalisations should be expected in the near-term from any of the combinations of transmissibility and immune escape that are consistent with the high growth rates observed.
- The proportion of Omicron infections that result in hospital admission cannot be known until there have been more hospitalisations (and analysis will need to consider the age profile of those infected and the immune history i.e. vaccination and past infection status). The number of people in hospital at any time will also depend on the length of stay, which will depend in part on severity of disease.
- Some early indications from South Africa suggest less severe disease in those hospitalised when compared to previous waves, though this likely reflects at least in part the characteristics of those being admitted to date, who are younger than in previous waves (low confidence). A modest reduction in severity would not avert high numbers of hospitalisations if growth rates remained very high.

- Although there are several unknown factors, preliminary modelling from SPI-M suggests that without any changes to measures in place, the number of hospitalisations from Omicron may reach 1,000 per day or higher in England by the end of the year (and still be increasing at that point).
- The overall scale of any wave of hospitalisations without interventions is highly uncertain, but the peak could reach several times this level. The peak is highly likely to be higher than 1,000 to 2,000 Omicron hospital admissions per day without intervention to slow the speed of increasing infections; for it to be below this level there would need to be only a small degree of immune escape and very high protection from boosters against Omicron.
- The impact of changes in transmissibility and immune escape on overall numbers of admissions is likely to be much more significant than the impact of any changes in severity (high confidence).
- There are other impacts from high levels of incidence aside from hospitalisations and deaths, including the morbidity burden in those who are not hospitalised and workforce absences. With very rapid doubling times a large wave could occur leading to synchronous absences from work.
- The overall scale of any wave of hospitalisations without interventions is highly uncertain, but the peak could reach several times this level. The peak is highly likely to be higher than 1,000 to 2,000 Omicron hospital admissions per day without intervention to slow the speed of increasing infections; for it to be below this level there would need to be only a small degree of immune escape and very high protection from boosters against Omicron.
- The faster the growth in infections at the point measures are introduced, the more admissions will increase in the period between action being taken and the number of admissions being affected. With lags of the order of two or more weeks, and doubling times of the order of three days, it is likely that, once hospitalisations begin to increase at a rate similar to that of cases, four doublings (i.e. a 16-fold increase) or more could already be "in the system" before interventions that slow infections are reflected in hospitalisations.
- It is highly likely that Omicron will account for the majority of new SARS-CoV-2 infections in the UK within a few weeks. Omicron may partially or largely replace Delta over this period, but the extent of this depends on the degree to which they are infecting different cohorts of people, which is not currently known. It is possible that both could continue to spread concurrently, which would mean that the Delta infections and hospitalisations would be in addition to Omicron ones. It is also possible that Omicron will completely displace Delta.
- Given the rapid increase, decision makers will need to consider urgently which measures to introduce to slow the growth of infections if the aim is to reduce the likelihood of unsustainable pressure on the NHS. The effectiveness of these will be dependent on the measures chosen, and also on behavioural responses. Evidence suggests that measures could be reintroduced with expectation of a similar level of adherence as has been seen in the past. Adherence is likely to be higher if messaging and policy have clear rationales and are consistent. Consistency across the UK may help with messaging.

- The generation time for Omicron is not known, but it is possible that it is shorter than for Delta, which would mean that case-based interventions (e.g. finding and isolating cases through contact tracing) become less effective because people become infectious sooner. This would increase the relative importance of population-based rather than case-based measures i.e. measures which affect everyone, not just those who are confirmed as being infected.
- Testing and self-isolation if positive remains very important. Testing before mixing events can help reduce the risk.
- Some international reports of 'superspreading' events (some of which include Omicron) also suggest a greater role for airborne transmission than has previously been the case, as it is less likely that Omicron could have spread to as many people as it has at those events by other routes (low confidence). This means that measures to reduce airborne spread such as ventilation, well-fitting masks and distancing or reduced density of people in indoor environments may be even more important.
- Nosocomial transmission is likely to be an even greater risk as a result of Omicron, particularly as hospitalisations increase. Measures will need to be put in place to reduce this risk including measures to reduce the risk of healthcare workers becoming infected and infecting others, and measures to reduce the risk of transmission between patients. Other vulnerable settings (e.g. care homes and prisons) will also need particular attention. Reducing nosocomial spread will be even more difficult with a more highly transmissible variant.
- Taking measures which slow or delay the wave of infections would allow more time for vaccination including ensuring increased coverage and boosting with existing vaccines. Laboratory neutralisation data will give an early indication of vaccine protection against Omicron infection over the next week, although data on infections and hospitalisations will be needed to fully understand the efficacy of different immune histories (different vaccines and/or past infections) particularly against severe disease. Vaccine and immune effectiveness against severe disease is likely to remain higher than protection against infection (medium confidence).
- Pharmaceutical interventions including antivirals will also continue to be important. Though antivirals should be used in combination where possible to reduce the risk of resistance developing, this will not be possible in the forthcoming wave of infections due to availability and lack of clinical trial data for combination approaches. Resistance monitoring, particularly in immunocompromised patients, will be needed and preparation should be made for combination therapies to be tested and rolled out as soon as practical.
- Full paper: SAGE 98 minutes: Coronavirus (COVID-19) response, 7 December 2021 - GOV.UK (www.gov.uk)

SPI-M Consensus Statement, 1 December

- The emergence of [the Omicron variant] in southern Africa is deeply concerning. Initial indications of its genetic variation compared to previous variants of this virus suggest it has potential for significant immune escape, although its full properties are unknown. While the evidence from South Africa is still emerging and subject to

a range of caveats, it is highly unlikely that the pattern of growth observed there would hold true if omicron did not have either a significant transmission advantage, significant immune escape, or both, or some other fitness advantage over the predominant variant (delta).

- The burden of disease for any wave of omicron infection will depend on size of the pool of people who are susceptible to infection and the severity of those infections. If omicron exhibits substantial immune escape, the pool of susceptible people in the UK could be large, and thus transmission could increase substantially. Any significant wave of infection, almost irrespective of immune escape, will spill over into hospitalisations. If initial estimates of transmission advantage and immune escape from South Africa are applicable to the UK population, there is the potential for a peak of infections much larger than that experienced in January 2021.

- If omicron in the UK combines increased transmissibility and immune escape, irrespective of severity, it is highly likely that very stringent measures would be required to control growth and keep R below 1. Delaying any wave of infections in such a scenario would allow more time for vaccines and therapeutics to be modified to combat omicron.

- Crude preliminary modelling has been conducted by two academic groups to consider the potential implications of a variant with immune escape (from both vaccine-induced and natural immunity) and transmission advantage. Any wave of significant infection, almost irrespective of immune escape, will spill over into hospitalisations, and ultimately deaths. If initial estimates of transmission advantage and immune escape from South Africa are applicable to the UK population, there is the potential for a very substantial peak of infections much larger than occurred during the winter wave of January 2021. Even if severity of omicron were half that of delta, the sheer number of infections could lead to significantly more pressures on health and care settings; currently there is no strong evidence that omicron infections are either more or less severe than delta infections.

- Due to the significant uncertainty and need for further data to emerge, SPI-M-O has discussed potential narrative scenarios, which cover the likely parameter space. SPI-M-O considers scenarios A, B or C from Table 1 *[see full paper]* a highly likely future for the UK. In contrast, scenarios D, E and F are each highly unlikely. There remains, however, considerable uncertainty in the current situation and likely or possible futures. As more information and evidence on omicron emerges, both globally and in the UK, some of these scenarios will become more and more unlikely, and even untenable. SPI-M-O will continue to consider these as more data emerge.

- If any of scenarios turns out to be the case, it is highly likely that very stringent measures would be required to control growth and keep R below 1. The scale of infections in any of these scenarios could be substantial and lead to unsustainable pressure on health and care settings; reducing the total number of infections will be easier than reducing the infection hospitalisation rate. Delaying any wave of infections in such a scenario would allow more time for vaccinations and therapeutics to be modified to combat omicron.

- Full paper: SPI-M-O: Consensus Statement on COVID-19, 7 December 2021 - GOV.UK (www.gov.uk)

NERVTAG: Antiviral drug resistance and the use of directly acting antiviral drugs (DAAs) for COVID-19

- The emergence of new SARS-CoV-2 variants such as Omicron (B.1.1.529) with the potential to (partially or fully) evade protection from vaccines and monoclonal antibodies increases the potential clinical and public health importance of small molecule DAAs. Omicron may remove some possible combination therapy options (i.e. small molecule plus monoclonal). Assuming small molecule DAAs retain activity against Omicron, it is important to preserve this activity i.e. avoid resistance.
- Two 'biological' DAAs against SARS-CoV-2 are currently approved for use in the UK – ronapreve and sotrovimab. Three small molecule DAAs against SARS-CoV-2 are currently either in use or close to use. Two nucleoside analogues; remdesivir (licensed) and molnupiravir (under conditional MHRA approval). BNT-00835231, Paxlovid (under review) a protease inhibitor.
- SARS-CoV-2 resistance to monoclonal antibodies is a significant problem, but very little evidence has been published on the potential for SARS-CoV-2 to develop resistance to small molecule antiviral agents. No studies or clinical trial data investigating resistance to molnupiravir or Paxlovid are available. Resistance has been reported for other coronaviruses to some DAAs, however the resistance phenotype impaired viral fitness.
- Resistance risk is increased by (i) increased use of antiviral drugs (increased virus-drug exposure), (ii) monotherapy, (iii) inadequate dosing, (iv) antiviral use in prolonged infections (e.g. in the immunocompromised).

<u>Recommendations</u>

- Although the propensity of current small molecule DAAs to develop SARS-CoV-2 resistance of clinical and public health significance is unknown, efforts to avoid, detect and mitigate resistance to these DAAs should be a high priority.
- DAA dosing and duration should consider the need to minimise the risk of resistance. These are the same principles used for other antimicrobial therapies. It may be appropriate to provide monitoring and support of adherence.
- Combination anti-viral therapy is, in theory, preferable to monotherapy in terms of a reduced risk of resistance and, possibly, improved clinical efficacy. The theoretical risk of promoting resistance is higher in patients who are immunocompromised, especially with inadequate therapy. There is, therefore, a pressing need to assess the safety, efficacy, and resistance potential of combinations of DAAs (and other) drugs.
- From a regulatory and business perspective, consideration should be given around how trials that aim to combine drugs can be conducted and how combinations can be licensed.
- Viral load and resistance monitoring, particularly in immunocompromised patients, will be needed to rapidly detect, evaluate, and mitigate emerging resistance.

- Methods and procedures should be established to quickly assess the "fitness" and the clinical and public health relevance of any emerging antiviral resistant viral variants.
- Prospective work is needed to establish which mutations can confer resistance on all potential DAAs, whether they carry a fitness cost for replication and transmission, and whether they affect disease. There is also a need to determine whether secondary mutations can subsequently restore fitness.
- Ongoing work is needed to establish whether newly emerging variants, such as Omicron, differ in their propensity to evolve resistance because of other unrelated mutations in their genomes and/or their increased replication rate (if confirmed).
- Full paper: NERVTAG: Antiviral drug resistance and the use of directly acting antiviral drugs (DAAs) for COVID-19, 8 December 2021 - GOV.UK (www.gov.uk)

COVID-19 evidence - round-up

This section aims to highlight a selection of the recent COVID-19 papers, reports and articles that are relevant to a Welsh context or contain new data, insights or emerging evidence relating to COVID-19. It may contain pre-print papers, which should be interpreted with caution as they are often not yet peer-reviewed and may be subject to change when published. The exclusion of any publication in this section should not be viewed as a rejection by the Technical Advisory Cell.

Omicron variant:

UKHSA Omicron variant risk assessment - 8 December

- UKHSA has published an updated risk assessment for the Omicron variant (see below), following an initial assessment on 3 December. A Red RAG status has been assigned to the variant's evasion of Infection and vaccine acquired immunity and therapeutic effectiveness (3 December only), while impact of the variant on transmissibility has been given amber status. Confidence levels have been upgraded since the earlier LOW confidence assessment to HIGH for increased growth advantage following emerging data, although it is still too early to determine whether transmissibility or immune evasion is the driving factor. Immune evasion has been upgraded to MODERATE confidence, although this does not yet consider the recently released neutralisation studies, which are still being assessed (see further below). There continues to be insufficient evidence to assess infection severity, due to the current lack of robust laboratory and real-world data.

8 December 2021 **Risk assessment for SARS-CoV-2 variant: Omicron VOC-21NOV-01 (B.1.1.529)** **UK Health Security Agency**

Indicator	Red, amber or green status*	Confidence level	Assessment and rationale
Growth advantage	Red	High	**Omicron is displaying a growth advantage over Delta** This assessment is based on analysis of UK data showing increased household transmission risk, increased secondary attack rates and increased growth rates compared to Delta. Omicron is likely to outcompete Delta in the UK and predominate. The observed growth advantage may be due to immune evasion or transmissibility. It is most plausible that it is a combination of both. The current growth rate implies either a substantial change in one parameter or at least moderate change in both (for example if transmissibility is similar to Delta, immune evasion must be substantial).
Transmissibility	Amber	Low	**Omicron is at least as transmissible as Delta** Increased transmissibility compared to Delta is biologically plausible with the presence of furin cleavage site and nucleocapsid changes associated in vitro with advantages for replication, as well as extensive changes to the RBD. Structural modelling suggests that the mutations present may increase human ACE2 binding affinity to a much greater extent than that seen for any other variant. However, there is as yet no demonstration of transmissibility as distinct from other contributors to growth advantage.
Immune evasion (including natural and vaccine derived immunity)	Red	Moderate	**Omicron displays a reduction in immune protection against infection (no data regarding severe disease)** Based on experience with other variants, laboratory data on individual mutations, and structural modelling, the mutations present are very likely to reduce antibody binding and include changes in all 4 neutralising antibody binding sites in the RBD and also in antigenic sites in the spike N terminal domain. New published neutralisation studies are being assessed. T cell epitope data are awaited. Whilst there are insufficient data to quantify either vaccine effectiveness or risk of reinfection in the UK, the observed growth, case distribution and early analyses in both SA and the UK are consistent with some loss of immune protection against infection. There are insufficient data to make any assessment of protection against severe disease.
Infection severity			**Insufficient data** There are insufficient data to assess severity, which is expected in the early period of emergence of a new variant.

* Refer to scale and confidence grading slide.

- Full paper: [8 December 2021 Risk assessment for SARS-CoV-2 variant: Omicron VOC-21NOV-01 (B.1.1.529) (publishing.service.gov.uk)]

UKHSA Omicron variant S gene target failure update - 8 December

- An updated briefing has been published following the below 3 December assessment. Prevalence of S gene target failure (SGTF), a proxy indicator for the Omicron variant, has quadrupled in the most recent week and as of Sunday was just below 1% of all cases in England.
- Based on SGTF numbers Omicron is rising fastest in London at 2.7%, followed by East Midlands at 1.6% and South East England at 1%. Areas in the north, south and west of England appear to have lower levels of Omicron and possibly more sporadic transmission.
- Full paper: [8 December SARS-CoV-2 variants of concern and variants under investigation (publishing.service.gov.uk)]

UKHSA Omicron variant technical briefing - 3 December

- A UKHSA variant technical briefing was also published earlier in the week focusing on the Omicron variant. As at 3 December, the SGTF proportion of cases had doubled from 0.1% to 0.2%. Delta can also have random SGTF (around 0.15% of Delta cases, decreasing to 0.06% recently) however any SGTF prevalence over ~0.1% is likely not Delta. The change in the most recent 7 days is pronounced with a growth rate of 141%, but previous growth rates span 90 days so more data needed for stable estimate.

- Regionally, SGTF is rising fastest in East Midlands, London and South East. This matches the location of confirmed Omicron cases.
- Overall there is a clear early signal of a molecular change in cases, likely led by Omicron. But note that Omicron remain a very tiny fraction of all cases (& sequenced cases) 99.8% of cases in England last week are Delta (of which ~23% are the Delta sub-lineage AY.4.2 and still rising slowly.
- Of the 22 confirmed cases, the age/sex distribution shows Omicron mainly affecting young & middle-aged adults. Only 1 case is in a child and 0 cases are in people aged 70+. 8/17 cases have known travel to a Red List country while 7/17 have unknown travel status (to date). There have been no hospitalisations or deaths in these cases.
- Where vax status is known (noting small numbers), 30% were unvaccinated, 10% partially vaccinated (1 dose) and 60% fully vaccinated (at least 2 doses)
- A large number of planned characterisation research studies are planned.
- Full paper: 3 December SARS-CoV-2 variants of concern and variants under investigation Technical Briefing 30 - Variant of concern: Omicron, VOC-21NOV-01 (B.1.1.529) (publishing.service.gov.uk)

PRELIMINARY DATA: Omicron Neutralisation studies

- At least five[1,2,3,4,5] different neutralisation studies containing experimental data have been made public this week, all confirming that neutralisation against Omicron infection from vaccines or natural infection is reduced to a greater extent than any previous variant of concern, with an average of between a 25 and 30-fold reduction in neutralisation from these studies compared to the original wild type SARS-CoV-2.
- The results of different neutralisation studies are difficult to compare and it is still too early to understand the discrepancies between the available studies, which include both live and pseudovirus studies. Nevertheless a consistent message is that boosters provide a level of antibody required to neutralise the virus.
- A Pfizer press release[4] (data not published at time of writing) suggests a third dose of their vaccine restores neutralisation to levels comparable to the effect of two doses against previous variants, providing credible evidence that a booster jab will protect against Omicron for the majority. However an unpublished German lab study[3] shows a more pessimistic outcome for the effect of boosters on restoring neutralising antibody activity, although it is based on a very small number of cases

[1] MEDRXIV SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer – Sigel, South Africa

[2] Preliminary Report - Quantification of the neutralization resistance of the Omicron Variant of Concern – Karolinska, Sweden

[3] Sandra Ciesek on Twitter - Germany (unpublished lab findings at time of writing)

[4] Pfizer and BioNTech P| Pfizer

[5] Janine Kimpel on Twitter: "First Omicron neutralization data from our lab using primary Omicron isolate from Tyrol

with a wide range of results. Regardless, boosters will likely still have value in bolstering cellular immunity which likely retains its efficacy against disease.

- It should be emphasised these results are **preliminary** and more laboratory data and accompanying analysis will continue to emerge, as well as real-world vaccine effectiveness data. All lab tests are single point tests, and cannot mimic the complexity and dynamics of the immune response in its entirety.
- While there is growing epidemiological evidence available from South Africa, it is still too early to know what proportion of these infections will lead to severe disease.
- Pfizer and BioNTech have also stated that they high confidence that if needed they can deliver an Omicron-based vaccine in March 2022[4].

Media reports of super-spreading events related to Omicron

- By 9 December, there had been media reports of Omicron super-spreader events in eight countries: Scotland, England[6], Portugal[7], Norway[8], Denmark, Australia[9], the USA[10] and India.
- All nine cases reported in Scotland have been linked to a single private event. No-one present had travelled overseas recently, which suggests community transmission. Two confirmed cases have been linked to a private party in Somerset and another 12 are suspected.
- There is a cluster of 13 cases at a Portuguese football club, where one player had recently returned from South Africa. There were 120 people at a Christmas party in Norway, where over 100 tested positive for Omicron. All are experiencing mild symptoms. In Denmark, 64 out of 150 guests at a community Christmas lunch have tested positive. Two people out of about 140 people on a boat cruise in Australia have tested positive for Omicron, whilst another three have tested positive for COVID-19. The Centers for Disease Control and Prevention are investigating a New York conference attended by about 53,000 people after one attendee tested positive for Omicron. A cluster of nine Omicron cases been reported from a wedding in India. The cluster includes is a family of four who had travelled from South Africa to attend the wedding.
- At a hospital Christmas party in Spain, 68 of the 173 attendees have tested positive for COVID-19 but the variant has not yet been identified[11].

[6] Somerset Omicron cases linked to party - BBC News

[7] Omicron in Europe: Where have cases of the new COVID variant been detected? | Euronews

[8] Norway Christmas party causes biggest Omicron outbreak outside South Africa | Euronews

[9] Fears over Omicron super-spreader event on Sydney boat party (yahoo.com)

[10] CDC zeroes in on anime convention to understand omicron variant (nbcnews.com)

[11] Nearly 70 medics at Spain hospital catch Covid after Christmas party | The Independent

ECDC: Implications of the further emergence and spread of the SARS-CoV-2 B.1.1.529 variant of concern (Omicron) for the EU/EEA – first update

- The evidence from the initial cases of this new variant that has been collated from around the world is limited, but suggests that the Omicron VOC may be associated with higher transmissibility than the Delta VOC, although robust evidence is still lacking. There remains considerable uncertainty related to vaccine effectiveness, risk for reinfections, and other properties of the Omicron VOC. Based on these factors, the probability of further introduction and community spread of the Omicron VOC in EU/EEA countries is currently assessed as HIGH.
- Current estimates on the severity of the infection associated with the Omicron VOC remain highly uncertain. The currently available evidence raises serious concern that the Omicron VOC may be associated with a significant reduction in vaccine effectiveness and increased risk for reinfections. The degree of protection against severe disease with the Omicron VOC conferred by past COVID-19 infection or by vaccination is not yet known. EU/EEA countries are still facing the severe impact of high numbers of cases of the Delta VOC. The impact of the further introduction and spread of the Omicron VOC could be VERY HIGH, but this situation needs to be evaluated as further information emerges.
- Based on the currently available limited evidence, and considering the high level of uncertainty, the overall level of risk for EU/EEA countries associated with the further emergence and spread of the SARS-CoV-2 Omicron VOC is assessed as HIGH TO VERY HIGH.
- To date, the Omicron VOC has already been introduced into many EU/EEA countries. Given the current limited evidence around this new variant and the concerns about its immune escape properties in relation to available COVID-19 vaccines and treatments, a multi-layered approach to delay the spread of this VOC in the EU/EEA is needed.
- Due to the ongoing circulation of the Delta VOC, EU/EEA countries are urged to give utmost priority towards the vaccination of people initially targeted by COVID-19 vaccination programmes who remain unvaccinated or who are not yet fully vaccinated. Countries should consider a booster dose for people aged 40 years and older, first targeting the most vulnerable and the elderly, and could then consider a booster dose for all adults aged 18 years and older at least six months after completion of the primary series.
- Non-pharmaceutical interventions (NPIs) that have proven to be very effective in reducing transmission of infection should continue to be implemented by countries based on an assessment of their epidemiological situation regarding the Delta VOC, and taking into account the uncertainty of the situation regarding the Omicron VOC. Physical distancing measures, ensuring adequate ventilation in closed spaces, the maintenance of hand and respiratory hygiene measures, the appropriate use of face masks, and staying home when ill all remain relevant.
- Enhanced contact tracing measures such as backward contact tracing and stricter management of contacts could help slow the establishment of the Omicron VOC in the country.

- Genomic surveillance remains of the utmost importance for early detection of the presence of the variant, to enable the following of epidemiological trends and guide containment measures.
- Temporary travel-related measures should be carefully considered in light of the latest epidemiological situation, and should be regularly reviewed as new evidence emerges. Such measures might include the testing and quarantining of travellers who have recently returned from affected countries and sequencing cases identified among travellers. Public information around the emerging situation and the public health measures in place for returning travellers from affected areas are important to raise awareness and support the effective implementation of these measures. However, given the increasing number of cases and clusters in the EU/EEA without a travel history or contact with travel-related cases, it is likely that within the coming weeks the effectiveness of travel-related measures will significantly decrease, and countries should prepare for a rapid and measured de-escalation of such measures.
- Full paper: Threat assessment brief - Emergence of SARS-CoV-2 variant B.1.1.529 - first update (europa.eu)

PREPRINT: Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa

- The first study examining the impact of the Omicron variant on reinfection risk in South Africa has been published. 35,670 suspected reinfections were identified among 2,796,982 individuals with laboratory-confirmed SARS-CoV-2 who had a positive test result at least 90 days prior to 27 November 2021.
- Overall, population-level evidence suggests that while the beta and delta waves were not associated with increased risk of reinfection and spread through higher transmissibility, the Omicron variant is associated with substantial ability to evade immunity from prior infection, with a risk of reinfection 2.39 times greater than the Delta variant (CI95: 1.88–3.11). In contrast, there is no population-wide epidemiological evidence of immune escape associated with the Beta or Delta variants. This finding has important implications for public health planning, particularly in countries like South Africa with high rates of immunity from prior infection. Urgent questions remain regarding whether Omicron is also able to evade vaccine-induced immunity and the potential implications of reduced immunity to infection on protection against severe disease and death.
- Limitations of the study are that it does not account for confounders such as waning levels of immunity; however the results align with what would be anticipated based on the large number of mutations carried by the Omicron variant. The study is also unable to provide insight into the robustness of vaccine-based immunity or infection severity from the available data. As a result of the low immunity from vaccination but high naturally acquired immunity the results are not directly comparable with more vaccinated countries like the UK and more data will be needed before the global impact of Omicron can be understood.
- Full paper: Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa | medRxiv

Omicron in Scotland - Evidence Paper

- Omicron is transmitting rapidly within Scotland and there is strong evidence that community transmission is widespread. The spread of in the UK appears to be similar to that seen currently in South Africa; although there are many epidemiological and societal differences between the two countries.
- Based on the data presented in this paper which is up to and including 9 December, it is highly probable that Omicron will outcompete Delta and become the dominant variant within Scotland very quickly, with the potential to cause high case numbers.
- The number of cases of the Omicron variant in Scotland can be tracked through S-gene target failure (SGTF), a feature of the results of positive PCR tests from Omicron infection, described in more detail later in this paper. As of 9 December, SGTF cases are already 13.3% of all PCR tests from Pillar 2 Lighthouse Labs, and we expect this to increase in the coming days and weeks. That proportion is rising exponentially
- Full paper: Omicron in Scotland - evidence paper - gov.scot (www.gov.scot)

Vaccines:

Lancet: Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAd Ox1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial

- This study investigated the reactogenicity (adverse reactions) and immunogenicity (immune response) of seven different COVID-19 vaccines as a third dose after two doses of Oxford–AstraZeneca; (ChAd) or Pfizer–BioNtech (BNT). The vaccines assessed were Oxford–AstraZeneca (ChAd); Pfizer–BioNtech (BNT); Moderna (m1273); Janssen (Ad26); Novavax (NVX); CureVac (CVn); Valneva (VLA).
- All vaccines tested boosted immunity after two doses of ChAd as measured by anti-spike IgG and neutralising assays, and six vaccines boosted immunity after two doses of BNT.
- Results were similar between those aged 30–69 years and those aged ≥70 years; no safety concerns identified. However, there were marked differences in response between specific booster vaccines. Cellular responses show that the mRNA vaccines and Ad26 show increased responses after two doses of ChAd and two doses of BNT; however, as demonstrated elsewhere, ChAd does not boost cellular responses after two doses of ChAd .
- Between study enrolment and the data lock on Aug 19, 2021, 21 participants (out of 912 reporting adverse effects) reported a PCR test result positive for SARS-CoV-2, with no hospitalisation.
- This trial has demonstrated the potential of all vaccines tested to boost immunity following an initial course of two doses of ChAd and of six vaccines following an initial course of BNT. All vaccines showed acceptable side-effect profiles, although some schedules were more reactogenic than others (created more side effects).
- These data are consistent with early data from other trials of homologous and heterologous third dose boosters. To date, both two doses of ChAd (79%) and two

doses of BNT (90%) have maintained highly effective real-world protection against hospitalisation and death after 6 months despite much higher absolute spike IgG levels for two doses of BNT than two doses of ChAd .

- These findings allow for flexibility to deploy heterologous or homologous third doses after initial ChAd or BNT vaccines and informed the subsequent JCVI advice around boosters.
- Full paper: Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAd Ox1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial

JAMA Network: Odds of Testing Positive for SARS-CoV-2 Following Receipt of 3 vs 2 Doses of the BNT162b2 mRNA Vaccine:

- This case-control study in Israel, which included 306,710 adults aged 40 years and older who had received 3 doses of the Pfizer vaccine, found a significant reduction in odds of SARS-CoV-2 infection within a few weeks of receiving the booster compared with receiving just the 2 primary doses. Comparing those who received a booster and those who received 2 doses, there was an estimated odds ratio of 0.14 (95% CI, 0.13-0.15) 28 to 65 days following receipt of the booster, or an 86% reduction in the odds of testing positive for SARS-CoV-2.
- The analysis also suggest that individuals who received the booster dose have a lower odds of hospitalization than those receiving 2 doses. However, these results should be interpreted with caution because a reduction in the odds of hospitalization was already evident in the first week after receipt of the booster when an effect would not be expected.
- The findings suggest that the waning of vaccine-induced protection against SARS-CoV-2 infection seems to be counteracted in the short-term by a third dose; however the study is limited by being short term and preliminary and longer-term monitoring will be required to determine the duration of immunity following the booster.
- Full paper: Odds of Testing Positive for SARS-CoV-2 Following Receipt of 3 vs 2 Doses of the BNT162b2 mRNA Vaccine

Journal of Psychosomatic Research: Side-effect expectations from COVID-19 vaccination: Findings from a nationally representative cross-sectional survey (CoVAccS – wave 2)

- An online cross-sectional survey aiming to investigate the percentage of people who thought side effects from COVID-19 vaccination were likely and factors associated with side-effect expectation has been published. The survey included 1,470 unvaccinated UK adults and was conducted in mid-January 2021.
- Concern about side effects is one of the most common reasons for refusing vaccination and side-effect expectations are known to predict perception of side effects. The authors suggest that public communications should emphasise the safety, effectiveness, and widespread uptake of vaccination, while promoting

accurate perceptions of the incidence and transitory nature of vaccination side effects.

- Most participants were uncertain whether they would experience side effects from a COVID-19 vaccine. Only a minority reported that side effects were very likely (9.4%). As systemic side effects are more common than this, such as fatigue (59% - 70% for Pfizer/BioNTech and AstraZeneca respectively), headache (52 - 68%), and fever (16 - 18%), the authors suggest experiencing unexpected side effects might affect uptake of a second dose. However side-effect expectations have increased since the MHRA's announcement that the AstraZeneca vaccine may be linked to unusual blood clots related to low blood platelets.
- Side-effect expectations were associated with: older age, being clinically extremely vulnerable to COVID-19, being afraid of needles, lower perceived social norms for COVID-19 vaccination, lower perceived necessity and safety of COVID-19 vaccination, and perceived lack of information about COVID-19 and vaccination. Lower perceived necessity of COVID-19 vaccination was also associated with greater side-effect expectations.
- Although adverse effects are more likely in younger people, the study found that older people had greater side-effect expectations. This may be reflective of the stage in the vaccination rollout in the UK at the time of this study (January 2021), with older people being offered the vaccine first. The authors suggest as rollout progresses side-effect expectations in younger age groups may increase.
- It is important that people are informed transparently and accurately about the likelihood and nature of side effects from vaccination. While educational interventions may be an attractive option, there is mixed evidence for their effect on vaccine uptake. Using simple infographics (e.g. pictographs) and improving the clarity and readability of information increase the accuracy of side-effect expectations.
- Communications should emphasise the safety, effectiveness, and widespread uptake of vaccination, while promoting accurate perceptions of the incidence of vaccination side effects such as fatigue, headaches and possibly fever and providing reassurance about the typically transitory and non-harmful nature of these side-effects.
- As this study is an observational study of a specific point in time, it cannot infer direction of causality between attitudes and beliefs and side-effect expectations. Further, like other self-reporting surveys this study may be subject to self-selection bias affecting the results.
- Full paper: Side-effect expectations from COVID-19 vaccination: Findings from a nationally representative cross-sectional survey (CoVAccS - wave 2)

ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome

- As part of the largest vaccination campaign in history, extremely rare side effects not seen in phase 3 trials, including thrombosis with thrombocytopenia syndrome (TTS), a rare condition resembling heparin-induced thrombocytopenia (HIT), were

observed as a side effect of the AstraZeneca vaccine, resulting in an alternative being offered to those under 40 years old.

- This study from Cardiff and Arizona State University suggests it is the viral vector – in this case an adenovirus used to shuttle the coronavirus' genetic material into cells – and the way it binds to platelet factor 4 (PF4) once injected that could be the potential mechanism for this side effect. The authors suggest this misplaced immunity could result in the release of antibodies against PF4, which bind to and activate platelets, causing them to cluster together and triggering blood clots in a very small number of people after the vaccine is administered.
- ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome (science.org)

Inequalities and indirect harms

UK Government report on progress to address COVID-19 health inequalities

- This final report provides a further update on cross-government work to address the disparities highlighted by the Public Health England (PHE) report COVID-19: review of disparities in risks and outcomes. The report also includes a summary of progress against recommendations from previous reports, lessons learnt from this work and an action plan for addressing some of the longer-term issues identified during the course of this project. The report also includes further analysis of how the impacts of COVID-19 changed for ethnic minority groups between the first and second waves of the pandemic.
- The report makes a number of recommendations around engaging ethnic minority groups, encouraging vaccination and improving ethnicity health data and statistics.
- Full paper: Final report on progress to address COVID-19 health inequalities - GOV.UK (www.gov.uk)

Treatments

MHRA approves Xevudy (sotrovimab), a COVID-19 treatment found to cut hospitalisation and death by 79%

- A second COVID-19 monoclonal antibody treatment, Xevudy (sotrovimab), has today been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) after it was found to be safe and effective at reducing the risk of hospitalisation and death in people with mild to moderate COVID-19 infection who are at an increased risk of developing severe disease.
- This follows a rigorous review of its safety, quality and effectiveness by the UK regulator and the government's independent expert scientific advisory body, the Commission on Human Medicines, making it the second monoclonal antibody therapeutic to be approved following Ronapreve.
- In a clinical trial, a single dose of the monoclonal antibody was found to reduce the risk of hospitalisation and death by 79% in high-risk adults with symptomatic COVID-19 infection.

- Based on the clinical trial data, sotrovimab is most effective when taken during the early stages of infection and so the MHRA recommends its use as soon as possible and within five days of symptom onset.
- It is too early to know whether the omicron variant has any impact on sotrovimab's effectiveness but the MHRA will work with the company to establish this. Sotrvimab is expected to be available in Wales from January 2022.
- Full paper: MHRA approves Xevudy (sotrovimab), a COVID-19 treatment found to cut hospitalisation and death by 79% - GOV.UK (www.gov.uk)
- In Wales Ronapreve, another Monoclonal antibody treatment, has been available for patients hospitalised with COVID since September 2021. Later this month access to Ronapreve will be extended to non-hospitalised patients who are considered to be at highest risk of progression to severe disease, hospital admission or death. The antiviral treatment, Molnupiravir may be offered to non-hospitalised patients aged 18 and above in this cohort if Ronapreve is contraindicated. Health Boards have been instructed to start to make these treatments available to non-hospitalised patients from 16 December.
- For patients not in the high risk group, Molnupiravir is only available via a new national study called PANORAMIC. This study, which is sponsored by the University of Oxford and funded by the National Institute for Health Research, opened for recruitment today (8/12/21). For inclusion individuals must have developed symptoms in the last 5 days, be COVID PCR positive and either aged 50+, or 18-49 years old with an underlying medical condition that can increase the chance of having severe COVID-19. The trial is open to individuals living anywhere in the UK.

Education

Rapid evidence review to inform safe return to campus in the context of coronavirus disease 2019 (COVID-19)

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted predominantly through the air in crowded and unventilated indoor spaces among unvaccinated people. Universities and colleges are potential settings for its spread.
- An interdisciplinary team from public health, virology, and biology used narrative methods to summarise and synthesise evidence on key control measures, taking account of mode of transmission.
- Evidence from a wide range of primary studies supports six measures:
- **Encourage vaccination—and make it easy** (aim for > 90% coverage and make it easy to get a jab).
- **Require masks indoors, especially in crowded settings**. If everyone wears well-fitting cloth masks, source control will be high, but for maximum self-protection, respirator masks should be worn. Masks should not be removed for speaking or singing.

- **Space people out** by physical distancing (but there is no "safe" distance because transmission risk varies with factors such as ventilation, activity levels and crowding), reducing class size (including offering blended learning), and cohorting (students remain in small groups with no cross-mixing).
- **Deliver clean indoor air** using engineering controls—ventilation (while monitoring CO2 levels), inbuilt filtration systems, or portable air cleaners fitted with high efficiency particulate air [HEPA] filters).
- **Test, trace and isolate** staff and students incidence of COVID-19 is high.
- **Support clinically vulnerable people to work remotely**. There is no direct evidence to support hand sanitising, fomite controls or temperature-taking. There is evidence that freestanding plastic screens, face visors and electronic air-cleaning systems are ineffective.
- The above six evidence-based measures should be combined into a multi-faceted strategy to maximise both student safety and the continuation of in-person and online education provision. Staff and students seeking to negotiate a safe working and learning environment should collect data (e.g. CO2 levels, room occupancy) to inform conversations.
- Full paper: Rapid evidence review to inform safe return to campus in the context of coronavirus disease 2019 | Wellcome Open Research

Wales COVID-19 Evidence Centre: Impact of educational and other COVID-19 restrictions on children aged 3-13 years

- This rapid review evaluated the impact of COVID-19 educational restrictions on children aged 3-13 identified within UK primary research.
- One rapid review and 13 UK primary studies were included.
- The evidence is weak and lacks recent and long-term data.

Findings suggested:

- There is some indication of various harms experienced by children from the imposed restrictions and changes in educational provision during the pandemic, but short and longer term evaluations of the harms are needed; harms cover well-being, mental and physical health, nutrition and attainment.
- There is almost no evidence on mitigations to offset the impact of the pandemic educational restrictions on the harms, representing a clear need for primary research. However, some schools may have introduced their own strategies which have not necessarily been documented and evaluated.
- Recommendations from the National Strategy for Educational Research and Enquiry (NSERE) enquiry, which did not focus on 3-13 year olds but was conducted in Wales), suggests the need to strengthen the home learning environment, in particular for bilingual and more vulnerable learners.

Epidemiology and Clinical

Age and Ageing: COVID-19 infection risk amongst 14,104 vaccinated care home residents: a national observational longitudinal cohort study in Wales, UK, December 2020–March 2021

- This study aimed to study infection rates of SARS-CoV-2 for older care home residents following vaccination and identify factors associated with increased risk of infection through using Welsh anonymised electronic health records and administrative data in the SAIL Databank. The study used a large cohort of 14,104 individuals and were also able to include information on frailty, previous infections and vaccination received.
- The authors observed a small proportion of care home residents with positive PCR tests following vaccination 1.05% (N = 148), with 90% of infections occurring within 28 days and 99% of infections occurring within 42 days. For the 7-day follow-up period they found a reduced risk of SARS-CoV-2 infection for vaccinated individuals who had a previous infection; hazard ratio 0.54 (95%CI 0.30, 0.95). For the 21-day follow-up period, they observed high hazard ratios for individuals with low and intermediate frailty compared with those without; 4.59 (95%CI 1.23, 17.12) and 4.85 (1.68, 14.04), respectively.
- Overall increased risk of infection after 21 days was associated with frailty, which saw up to an almost 5-fold increase. While it is well known that there is a delay following immunisation for the vaccine to be effective, most infections occurred within 28 days of vaccination, suggesting extra vigilance and precautions to reduce transmission risk for this highly vulnerable population should be taken in this time frame. The study also found a large and statistically significant reduced risk for vaccinated individuals who had previously had a SARS-CoV-2 infection.
- The study only had a limited follow-up time and subsequently a small number of infections. At the time of analysis information was not included on second doses because of small numbers; however this will be added to a future analysis which could also include considerations of background prevalence and other measures of frailty.
- Full paper: COVID-19 infection risk amongst 14,104 vaccinated care home residents: a national observational longitudinal cohort study in Wales, UK, December 2020–March 2021 | Age and Ageing | Oxford Academic (oup.com)

Wales COVID-19 Evidence Centre Review: Active and Prospective Long-COVID Research in Wales

- This summary of research studies into Long COVID aims to describe the current and prospective work that is happening in Wales. It also aims to highlight opportunities for participation in this research, both for people with Long COVID, and health care professionals involved in their care.
- The UK NIHR commissioned 15 studies into Long Covid (starting June 2021 onwards).
- There are 4 Long Covid studies currently ongoing in Wales, including:

  - PHOSP-COVID, which is a UK wide study aiming to understand the long-term effects on patients who have been hospitalised with COVID-19 and the ongoing medical, psychological and rehabilitation needs of those patients.
  - HEAL-COVID which is a UK wide clinical trial aiming to identify treatments that may be beneficial for people discharged from hospital after recovering from COVID-19.
  - REGAIN which is looking to evaluate potential treatments for Long COVID. This is a clinical trial evaluating an intensive, on-line, supervised, group, home-based rehabilitation programme to support long-term physical and mental health recovery (REGAIN) vs. best-practice usual care in patients discharged from hospital after COVID-19 infection.
  - The 'Understanding Experiences of Long COVID in Families' study which is a qualitative study using interviews with patients to better understand people's experiences of Long COVID, how it may be changing family life and to find out why some families have different experiences to others.

- The following studies are under set up in Wales:
  - LOCOMOTION, which looks to bring together Long COVID teams from different areas of UK and to develop best practice guidelines for the assessment and management of individuals with Long COVID.
  - LISTEN, which is developing an intervention consisting of a package of self-management support, co-designed with individuals living with long COVID and other stakeholders.
  - The immunologic and virologic determinants of Long-COVID study, which aims to provide new insights into the cause of Long COVID and to explore whether Long COVID results from the impact of the coronavirus on the body's immune system.
  - EXPLAIN, which looks to understand why some individuals with Long COVID continue to struggle with breathlessness and have a reduced ability to exercise despite usual tests, including computerized tomography (CT) scans, being normal.
  - CICERO, which looks at why patients develop long term problems with memory, attention or other cognitive function (sometimes called 'brain fog') following COVID-19 infection.

- Further information and support for prospective participants, professionals and researchers can be found via the Health and Care Research Wales Support and Delivery Service.

Wales COVID-19 Evidence Centre Review: Effectiveness of service delivery interventions for adult orthopaedic patients on a surgical waiting list

- This rapid review summarised evidence for supply-side service delivery innovations (i.e. those aimed at increasing the surgical workforce and equipment, utilisation of

specialist centres, and improving capacity) to help reduce the backlog that would be relevant to adult orthopaedic patients on a surgical waiting list.

- 17 primary studies were identified, none addressed the impact of the Covid-19 pandemic.
- Most of the evidence identified was derived from non-randomised uncontrolled before and after studies with serious methodological limitations and risk of bias. Complex interventions make it hard to distinguish individual component effects.

Findings suggested:

- Potential changes to reduce wait times to address the surgical backlog should consider a multi-component approach acknowledging local context
- Lean and Six Sigma methodologies (designed to increase the efficiency of a process by reducing wasteful steps), reconfiguration of the surgical pathway and the provision of additional resources could be considered as part of the multicomponent approach.
- Further research and evaluation of strategies introduced to address the backlog from the Covid-19 pandemic is needed to inform ongoing policy decision-making in this area.

Non-pharmaceutical Interventions

Gov.uk: Events Research Programme: Phase II and III findings

- The UK Government has published the Phase II and III findings of its Event Research Programme, aimed at researching audiences returning to mass events to examine the risk of transmission of COVID-19 from attendance at events and explore ways to enable people to attend a range of events safely.

  Findings - Environmental and Behavioural studies

- The studies demonstrate that environmental and behavioural risk factors associated with COVID-19 transmission at events are complex and contextual. The studies assessed air quality by measuring CO2 across 179 spaces in ten venues, as CO2 is mainly present in exhaled breath and can identify spaces with poor air quality from overcrowding or insufficient ventilation. Poor air quality in events with multiple occupants indicates a higher airborne transmission risk.
- The studies observed good air quality, for the given occupancy levels, in nearly all venues, however there were situations leading to poor air quality in some spaces: mostly due to pockets of overcrowding but occasionally due to ventilations strategies needing improvement. Key measures of average and maximum CO2 levels and peak crowd densities varied significantly between different events and during them. The average CO_2 levels during an entire event were below 800 ppm in 170 out of 179 monitored spaces.
- Air quality studies were complemented by studies focusing on attendee behaviour during the event. Studies showed that increasing the number of people in a given

space reduces the ability to physically distance and increases the risk of close contact with others. Adherence to safety measures including physical distancing and face covering usage were higher at events or locations within an event where they were required rather than discretionary.

- Individual risk while attending an event is dependent on social interactions, on the interaction with the environment, and on the individual journey through an event. It is not yet possible to directly quantify the passive risk of inhaling aerosol particles that carry the virus from ambient air. However, risk is increased with prolonged and repeated exposure to poor air quality, insufficient ventilation, reduced distancing between individuals or limited compliance with face covering. It was found to vary significantly among venues and even within the same event, implying that customers can choose lower risk environments and behaviours to reduce their personal risk. Risk assessments and possibly additional mitigations should be considered separately for staff.
- Analysis of the data from ERP continues and further investigation of key risk factors will be used for further modelling and to inform policy guidance. Venues and event organisers should consider their ventilation strategy, occupancy, operations, space utilisation, and people movement within an overall risk assessment tailored to each venue. Appropriate mitigations, such as an enhanced ventilation strategy, must be part of a hierarchy of controls including face coverings and reducing crowding.

Findings - Self Controlled Case Series study

- Data were obtained for a sample of people who both attended a Phase III ERP event, and had any COVID-19 test result recorded in NHS Test and Trace in the 16 days following attendance at the event. The proportion of attendees for whom attendance data were available varied from approximately 3% at some events to greater than 90% at others. The rate of positive testing for COVID-19 was compared within person, between a 7 day high risk period following attendance at an event with the subsequent 7 day period when infection risk is assumed to be unaffected by attendance at the event. The rate for negative testing was also calculated to determine any bias in testing trends over the observation period.
- Approximately 1.7% of attendees, for whom data were available, tested positive for COVID-19 during their 16 day study period. The results tend to show that there was little evidence of increased transmission by attendance at the following categories of events: mainly outdoor seated, mainly outdoor partially seated or the indoor seated theatre events studied.
- Caution is needed when interpreting these findings. For example, some theatre events were run at or below 50% of normal full capacity and involved low numbers of attendees, meaning the study was unable to rule out a potentially important increased risk of transmission. Bearing in mind the findings of the environmental and behavioural studies, these results may not generalise to other contexts where venue characteristics and individual/crowd behaviour may be different.
- Attendance at the mainly outdoor unseated events studied (Goodwood, Latitude and Tramlines) was associated with a 1.7 fold increased risk of COVID-19 transmission amongst attendees (95% confidence interval between 1.52 and 1.89). For context, the risk of infection in the baseline period was ~0.9% for Latitude

attendees in the study; a 70% increase would take this risk to 1.53%. This confidence interval means the estimate of 70% is robust due to the large number of attendees (over 2000) at these events. Reasons for this difference in transmission risk are likely to be multifactorial and could include behaviour whilst at the event, overall event size and duration or mode of travel to and from the event. It should also be noted that these results are set against the background of a particular epidemiological situation, and the possibility remains that new variants arise that are more transmissible and possibly less responsive to vaccines than those encountered in our studies, which would change transmission risk.

- Across all events, where attendee COVID-19 vaccination status was self-reported, 87% of people with a positive COVID-19 test result during the study period were unvaccinated.

NHS App trial and COVID-status Certification Learnings

- The NHS COVID Pass was introduced for the EUROs games in Phase II as a means for certification, alongside using a vaccination letter ordered from 119 or nhs.uk to verify COVID status, and this method was used for all Phase III events. In Phase II (EUROs only) and III individuals were required to show proof of:
    - a negative test (lateral flow) taken within 24-72 hours of entry to a venue (in Phase III it was 48 hours)
    - vaccination (two doses of a U.K. approved vaccine plus two weeks); or
    - natural immunity from a prior positive PCR test (up to 180 days post PCR test)
- Testing of the NHS COVID Pass generated insights on user journey and communications, as well as testing infrastructure, experience of organisers and operational delivery at venues. Insights from the wider testing of certification through the ERP have informed the UK Government proposal for mandatory vaccine certification in a Plan B scenario.
- These pilots found compliance with certification protocols improved with clearer and more consistent communications, which aided the avoidance of confusion. They demonstrated the importance of having properly trained stewards who are equipped to rapidly and accurately verify COVID status, in order to minimise queuing and associated safety and security concerns.
- Full paper: Events Research Programme: Phase II and III findings - GOV.UK (www.gov.uk)

Aggressive containment, suppression, and mitigation of covid-19: lessons learnt from eight countries

- An article in the BMJ argues aggressive containment of community transmission is the optimal strategy in emerging pandemics to save lives and protect the economy and achievable in the absence of vaccines and treatments.
- The three distinct strategic approaches in the study were defined as:

- Aggressive containment—countries aimed to eliminate community transmission and achieved elimination status for 28 consecutive days by implementing public health interventions
- Suppression—countries aimed to suppress and minimise community infections by implementing public health interventions
- Mitigation—countries aimed to avoid overwhelming health systems by flattening the epidemic curve or achieving herd immunity in the population. The public health interventions focused on protecting vulnerable and high risk groups while allowing transmission among low risk groups.A comprehensive package of public health interventions needs to be implemented stringently with support measures for mitigating the adverse effects and increasing capacity
- The three strategies have their own benefits, challenges, and trade-offs:

Strategy	Benefits	Challenges	Trade-offs
Aggressive containment	Lowest deaths per million. Quicker economic recovery.	Requires resources and infrastructure to build increased capacities in a short time.	Stringent mobility restrictions may increase unemployment and reduce access to social and health services. Restriction of civil liberties and raises concerns about privacy infringement when aggressive contact tracing measures are taken.
Suppression	Reduces covid-19 burden in the short term, thus avoiding overwhelming the health system.	Easing control measures before eliminating community transmission can lead to resurgence and excessive deaths. Recurrent public health interventions can cause fatigue, undermining the effectiveness of the interventions.	Stringent mobility restrictions may increase unemployment and reduce access to social and health services.
Mitigation	Preserves freedom of movement.	Older people are not completely protected from infection, so the health system can be overwhelmed, resulting in excessive deaths.	High death rates comparable to countries following the suppression strategy. But contrary to common belief, they also suffered from economic contraction and a slow recovery in the first year.

- Although factors such as culture, demographics, and geography have contributed to how the pandemic and responses unfolded, countries that opted for aggressive containment had lower deaths per million than those that took other approaches. Successful containment requires countries to take immediate action in response to emerging outbreaks and clearly define the targets for relaxing interventions
- Success is underpinned by trust in policy makers and government and community engagement and facilitated by strong political commitment, well prepared public

health systems, and scientific input into policy making. By engaging the community and implementing privacy safeguards, contact tracing applications offer faster tracing and ring-fencing, and is therefore postulated to contribute to successful containment.

- Aggressive containment might not be sustainable in the long term. A more sustainable approach which amalgamates acceptable levels of community transmission and high vaccination rates may be the best way forward. As more countries, including those successful in containment, transition to covid-19 endemicity, continuing investments and efforts are needed to reduce inequalities, enhance health system capacities, and strengthen public health preparedness in the event of potential emergent strains and waning vaccine immunities.
- Full paper: Aggressive containment, suppression, and mitigation of covid-19: lessons learnt from eight countries | The BMJ

Wales COVID-19 Evidence Centre Review: Infection control and prevention measures in care homes

- This rapid review explored evidence relating to adverse outcomes from infection prevention control (IPC) practices to help inform policy recommendations and identify gaps within the literature where further research can be prioritised.
- 15 studies were identified: 14 primary studies and one rapid review.
- There was a lack of high-quality evidence from the included studies. Confidence in the strength of evidence was rated as 'low' overall.

Findings suggested

- IPC policies should be clear, concise and tailored to care homes and domiciliary care settings
- Increased attention to workforce planning is needed to ensure adequate staffing and to reduce individual burden
- Restrictions (e.g. visitation) for care home residents needs to be balanced by additional psychological support
- Further research with robust methods in this area is urgently needed especially in the domiciliary care setting