ARHAI Scotland

Antimicrobial Resistance and Healthcare Associated Infection

NHS National Services Scotland

Rapid review of the literature: Assessing the infection prevention and control measures for the prevention and management of COVID-19 in health and care settings

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Version history

Version	Date	Summary of changes
1.0	19/3/2020	Assessment of the emerging COVID-19 evidence base, includes literature identified up to 16 March 2020.
1.1	3/4/2020	Assessment of the emerging COVID-19 evidence base, includes literature identified up to 30 March 2020.
1.2	20/4/2020	Assessment of the emerging COVID-19 evidence base, includes literature identified up to 13 April 2020.
3.0	15/5/2020	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 11 May 2020.
4.0	24/6/2020	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 15 June 2020.
5.0	23/7/2020	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 20 July 2020
6.0	2/9/2020	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 31 August 2020
7.0	2/10/2020	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 28 September 2020
8.0	05/11/2020	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 02 November 2020
9.0	04/12/2020	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 30 November 2020
10.0	15/01/2021	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 05 January 2021
11.0	05/02/2021	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 01 February 2021
12.0	12/03/2021	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 01 March 2021
13.0	09/04/2021	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 29 March 2021
14.0	07/05/2021	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 26 April 2021
15.0	11/06/2021	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 31 May 2021
16.0	15/07/2021	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 05 July 2021
17.0	11/08/2021	Monthly assessment of the emerging COVID-19 evidence base, includes literature identified up to 02 August 2021

Contents

1. Aim

To provide a rapid review of the scientific evidence base to inform the infection prevention and control measures required for the prevention and management of COVID-19 in health and care settings.

2. Objectives

Objectives for the rapid review were to establish the following:

- The epidemiology of COVID-19;
- The personal protective equipment (PPE) requirements;
- The requirements for hand hygiene;
- The environmental survivability of COVID-19;
- The requirements for cleaning/decontamination of the care environment;

3. Methodology

The methodology for this rolling rapid review was developed to ensure frequent and timely assessment of the emerging evidence base could be provided.

Academic databases (Medline and Embase) were first searched on 5th March 2020 to identify relevant literature (see Appendix 1 for search strategies). Searching was also conducted on the pre-print database, medRxiv (via NIH icite). Additional grey literature searching was conducted which included searching online resources from the World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC), Public Health England, UK, Scottish, Canadian and Australian Government guidance, the UK Scientific Advisory Group for Emergencies (SAGE), the Novel and Emerging Respiratory Virus Threats Group (NERVTAG).

Studies were excluded if they were published pre-2000, if they were published in non-English language and if they were animal studies.

Inclusion criteria was kept broad owing to SARS-CoV-2 being a novel pathogen, any study design was considered. Screening was undertaken by two reviewers, any uncertainty over the relevance of an article was decided by agreement between the two reviewers. As this was a rapid review, evidence was critiqued but not formally graded with the use of an appraisal tool, meaning that graded recommendations were not feasible.

The SIGN50 critical appraisal system is used for ARHAI Scotland systematic reviews and while time constraints meant individual studies were not entered into SIGN50 checklists for this rapid review, the SIGN50 principles were applied to critical analysis of the evidence base and data extraction from studies was entered directly into evidence tables developed for the rapid review.

3.1 Evidence updates

The emerging evidence base on COVID-19 is rapidly changing. To account for this, published literature is screened on a weekly basis and weekly evidence updates produced. Updates to the rapid review will be made on a monthly basis, or if the evidence base indicates that a change to recommendations is required.

4. Epidemiology

4.1 Transmission routes

Early analysis of the transmission of COVID-19 was thought to occur mainly via respiratory droplets[1-10] generated by coughing and sneezing, through direct contact[1, 3, 6-11] and indirect contact with contaminated surfaces.[1, 6, 7, 9, 10] These transmission routes were supported by early National[12-14] and international guidance.[15, 16] The World Health Organization (WHO) in a scientific brief published July 2020 supported that the main mode of transmission was via respiratory droplets, which are expelled when an infected person coughs, sneezes, talks or sings.[17] Transmission through contact with contaminated surfaces (fomite transmission) is considered possible due to the presence of COVID-19 viral RNA on surfaces (see section 7 – survival in the environment) however there has so far been no published evidence to demonstrate singularly in real-life scenarios, as it is impossible to separate the contribution from other transmission modes.

As the pandemic has progressed, there have been growing calls to acknowledge a potential airborne transmission route. The European Centre for Disease Prevention and Control (ECDC) describe transmission as occurring via respiratory droplets, either by being inhaled or deposited on mucosal surfaces, including aerosols produced when coughing and speaking, however acknowledge that the relative role of large droplet, aerosol and fomite transmission remains unclear.[18] The US Centers for Disease Prevention & Control (CDC) stated in a scientific brief published 7th May 2021 that exposure to respiratory fluids occurs via inhalation of fine droplets and aerosol particles, deposition of droplets and particles onto exposed mucous membranes, as well as touching mucus membranes with hands soiled by exhaled respiratory fluids.[19] Risk of transmission is considered to be greatest within three to six feet of an infectious source where the concentration of emitted particles is greatest. The CDC also stated that airborne transmission may be possible under special circumstances, specifically: in enclosed spaces where there is inadequate ventilation or air handling, during prolonged exposure to respiratory particles, and where 'increased exhalation' may have occurred (exercising, singing, shouting).[19] The WHO published an updated scientific summary of COVID-19 transmission in December 2020, stating that outside of medical facilities, in addition to droplet and fomite transmission, aerosol transmission could occur in specific settings and circumstances, particularly in indoor, crowded and inadequately ventilated spaces, where infected persons spend long periods of time with others.[20] More recently, in their interim IPC guidance published 12th July 2021, WHO stated that the virus spreads mainly between people who are in close contact with each other, typically within 1 metre (short-range).[21] The CDC state that there are several well-documented examples in which transmission appears to have occurred over long distances or times, however the references provided in the report, which are largely from outbreak reports in overcrowded community settings (restaurants, recreation, gyms) do not provide clear evidence of 'traditional' airborne transmission (defined as long distance transmission of respiratory aerosols). The evidence base for possible human-human airborne transmission, as presented by the CDC, is largely from community settings.[22-24] Outbreak reports are, by their nature, prone to many methodological limitations (e.g. self-report bias, publication bias, lack of robust data) however continue to be the main source of evidence regarding transmission modes. In the absence of robust evidence for airborne transmission, a more accurate description of what might be facilitated in those specific circumstances as described by both the CDC and WHO is 'short-range aerosol' transmission, whereby poor ventilation combined with overcrowding/close contact in small spaces provide the conditions for respiratory aerosols to remain suspended in the air thus increasing the risk of transmission. This is a move away from the historical dichotomy of droplet vs. airborne, instead acknowledging that an aerosol produced at source will also present the risk of being transmitted at close range (e.g. within 2 metres). The UK

Scientific Advisory Group for Emergencies (SAGE) in April 2021 stated that evidence suggests airborne transmission is most likely in poorly ventilated spaces but that applying full conventional airborne precautions throughout a hospital is neither practical nor likely to be necessary.[25] Currently there is no clear evidence of 'traditional' long-range airborne transmission of SARS-CoV-2 from outbreak reports. From unpublished Scottish outbreak reporting from acute care settings it is clear there is large variation in the size and duration of outbreaks, with some units experiencing just a few cases per outbreak cluster and others in the double figures. Consistently large outbreaks might be expected with a predominantly airborne transmission mode however there are many confounding factors that could impact the transmission rate. Prolonged shedding in a patient could also theoretically maintain an outbreak, inability of some patients to wear facemasks, breaches in control measures such as physical distancing, hand hygiene, adequate cleaning and PPE use and delays in recognising symptoms can also significantly contribute to the transmission rate. All of these have been reported consistently during outbreaks and are further fuelled by increasing inpatient numbers and staffing shortages. There are wards in which contact and droplet precautions were applied for managing COVID-19 patients with no onwards transmission. Without a detailed epidemiological investigation, ideally with whole genome sequencing, it is very challenging to obtain data from outbreak reports that provides reliable and valid assessment of the potential transmission modes.

It must be acknowledged that further research is required to determine the potential contribution of aerosol transmission of respiratory viruses, acknowledging a spectrum of particle sizes. This would include analysis of, for example, experimental studies that do not involve actual human-human transmission but demonstrate a theoretical aerosol 'potential'. These include experimental laboratory studies designed to assess visualisation of droplet expulsion from the human mouth/nose, mechanically-generated aerosol studies where the air is experimentally seeded with viral particles, animal studies involving an artificially infected donor and recipient, and air sampling studies where presence of viral RNA (and subsequent cell culture) is used as a proxy for transmission risk. These studies collectively demonstrate a potential for air-mediated transmission but are generally considered low quality evidence due to concerns regarding their validity and representativeness (particularly with regard to the animal studies).

Air sampling studies conducted in COVID-19 healthcare environments have shown mixed results. A number of international studies (South Korea, Ireland, China, Iran, Italy, Canada , Brazil) returned negative results for the presence of viral RNA by RT-PCR in air samples collected from active air sampling[26-36] or settle plates[37] in ICUs, single patient rooms, multi-bed bays, general corridors, fever clinics, EDs, rooms of long term care facilities, treatment rooms

and throat swab sampling rooms, and 'clean' areas.[38, 39] In these studies, patients were often intubated, mechanically ventilated, on non-invasive ventilation or receiving high-flow nasal oxygen (HFNO). The distance between the air samplers and the patients varied from 0.6m to 5m. Symptom severity, number of days since symptom onset, and environmental ventilation provision in these studies also varied. There has been an attempt to assess the influence of ventilation on the observed outcomes of air sampling (and environmental sampling);[35] this is a methodologically challenging task with many confounding factors to account for.

Studies that have reported positive air samples are also heterogeneous in terms of patient symptoms, duration since symptom-onset, ventilation provision, and distance of sampler placement from patients. Positive air samples have been reported in isolation rooms and corridors of COVID-designated hospitals,[40, 41] airborne isolation rooms of general wards,[42, 43] PPE-removal rooms,[44-46] ICUs,[38, 45, 47-49] hospital corridors,[38, 46] bays,[50] long-term care rooms,[49] and single patient rooms.[50-54] Active air sampling in 2 Wuhan hospitals demonstrated positive results in PPE-removal rooms, which led the author to suggest resuspension of virus-laden aerosols from the surface of contaminated PPE was contributing to air contamination; very low/non-detectable concentrations of viral RNA was detected in COVID-19 ICUs.[44] Active air sampling in an ICU treating 15 patients with severe disease and in a general ward treating 24 patients with mild disease returned positive results in 35% of samples collected from the ICU and 12.5% of samples from the general ward.[47] A study at a hospital in China detected viral RNA in one out of 12 bedside air samples collected at a distance of 0.2 metres; breath condensate samples from the patient were also positive however it is not possible to distinguish droplet from airborne detection in this study, and there was no data provided regarding the clinical procedures conducted in the room before or during sampling.[55] Active air sampling in a London hospital detected viral RNA in samples from multiple patient areas however repeat sampling returned positive results in 3 areas only.[56] When testing was carried out in the presence of tracheostomies, only 1 of 8 samples was positive. One out of 12 active air samples taken from COVID-19 patient rooms in a hospital in Wuhan tested positive within 10cm of a patient undergoing endotracheal intubation for invasive mechanical ventilation.[51] Four out of 55 samples taken <1m from patients at 8 hospitals in England tested positive; 3 of the 4 patients were undergoing AGPs at the time (CPAP, non-invasive ventilation).[50] One study has demonstrated the presence of viral RNA in the filters of exhaust ducts located ~50 metres from COVID-19 patient rooms; samples were collected by placing cut sections of HEPA filter into viral transport medium.[57] Identification of viral RNA on air ducts/ventilation grilles has been highlighted as potentially indirect evidence of aerosol production, however unpicking the potential contributors to contamination in these studies is challenging.[58]

Notably, there is large heterogeneity in the sampling method employed in these studies, and no recognised standard for air sampling, which may impact the observed outcomes. The ventilation systems and modifications also differed significantly between settings. A major limitation in these studies is the lack of detail regarding the types, timing and duration of clinical procedures carried out, therefore limiting a full understanding of their potential impact on the observed sampling results. Positive air samples from ICUs/patient rooms may be a reflection of the higher aerosol risk that is related to aerosol-generating procedures (AGPs) that are conducted in these high risk clinical settings. Conversely, the observed negative air samples in some studies may be impacted by the ventilation provision, as a higher air change rate (the number of air changes in the space per hour) has been shown to be associated with a lower infection risk in modelling studies.[59] A living systematic review assessing air sampling was unable to identify any pattern between the type of hospital setting (e.g. ICU versus non-ICU) and RT-PCR positivity in air samples.[60]

Few studies have tested viability of air samples. Four out of 6 samples taken from a single hospital room containing 2 COVID-19 patients at a hospital in Florida were positive; inoculation in Vero E6 cells showed cytopathic effect, suggesting viability.[61] Again, this study does not detail the types of patient care activities performed in these rooms. Most studies have been unable to identify viable virus or viral replication in air samples collected from hospital inpatient rooms.[43, 49, 50, 52, 54, 56, 62, 63] Viral culture is often used as a proxy for infectivity however there is no certainty that individuals with non-culturable samples are not infectious.

Aerosol-generating procedures

Aerosol-generating procedures have been associated with an increased risk of transmission of previous coronaviruses (SARS-CoV and MERS-CoV)[16, 64] and a number of AGPs (mostly airway management) have been implicated as risk factors for transmission of SARS-CoV-2 to health and care workers (HCWs)[9, 65] however attributing risk to specific procedures with any level of certainty is challenging. The concept of an 'aerosol generating procedure' arose following the study of SARS-CoV transmission events where it was observed that a pathogen, which was consistently associated with droplet or contact transmission, appeared to have the potential to infect HCWs via the airborne route during specific procedures. This is reflected in the World Health Organization's (WHO) definition of an AGP which states that AGPs create the potential for airborne transmission of infections that may otherwise only be transmissible by the droplet route.[66] It should also be recognised that as well as producing aerosols, these procedures produce a spectrum of droplet sizes including larger droplet particles.[67-69]

The WHO further defines an AGP as those procedures which result in the production of airborne particles (aerosols).[66] Particles which they describe as being <5 micrometres (μm) in size and as such can remain suspended in the air, travel over a distance and may cause infection if inhaled.[66] These particles are created by air currents moving over the surface of a film of liquid, the faster the air, the smaller the particles produced.[66] Using this definition there are potentially many medical or patient care procedures which could be classed as 'aerosol generating' but whether they lead to an increased risk of respiratory infection transmission is a different and important question. The 2014 WHO guidance is specific in its wording, outlining that '*some procedures potentially capable of generating aerosols are associated with increased risk of SARS transmission to health-care workers*' and they outline that, regarding pandemic and epidemic prone acute respiratory infections, it is for these procedures that airborne precautions should be used.[66] Medical and patient care procedures should be assessed based not only on their capacity to generate aerosols but also on their ability to generate infectious aerosols and an association with relevant transmission events. For example, whilst it has been observed under experimental conditions using healthy volunteers that continuous positive airway pressure ventilation (CPAP) and high flow nasal oxygen delivery (HFNO) (both AGPs) may produce less aerosols than coughing, there was no assessment of the generation of infectious aerosols in these scenarios tested.[70] Health Protection Scotland conducted a review of the evidence base for a number of clinical procedures for their consideration as AGPs in relation to increased risk of respiratory infection transmission, in collaboration with the Department of Health and Social Care's New and Emerging Respiratory Virus Threat Assessment Group (NERVTAG).[71] Additional clarity was provided regarding dental procedures and surgical/post-mortem procedures; risk during dentistry is related to the use of high speed devices such as ultrasonic scalers and high speed drills. In surgery/post-mortem, risk is related to the use of high speed cutting if this involves the respiratory tract or paranasal tissues.

Variants of concern

In December 2020, a new SARS-CoV-2 variant (Variant of Concern (VOC) 202012/01), also known as B.1.1.7 lineage, was identified in the south west of England. In June 2021 the World Health Organization released new nomenclature for variants of concern, using the Greek alphabet. B.1.1.7 (aka Alpha) differs by 29 nucleotide substitutions from the original Wuhan strain, having multiple spike protein mutations with one of the S-gene mutations deleting two amino acids at positions 69 and 70 causing a reproducible S-gene target failure (SGTF) in the Thermofisher TaqPath assay used in the UK Lighthouse laboratories.[72] The observed rapid increase in COVID-19 cases overall in the south west of England was temporally associated

with the emergence of the new variant in this area in November 2020. SAGE/NERVTAG stated there is 'high confidence' that this variant is spreading faster than other SARS-CoV-2 virus variants currently circulating in the UK, with apparent evidence that is consistent with an increase in transmissibility being a factor. Preliminary evidence suggested the possibility of lower Ct values in those infected with this variant, which is consistent with an increase in viral load, [73] however this has not been demonstrated in more recent studies. There is so far no evidence to suggest an increase in severity of symptoms or mortality associated with this new variant. Since the emergence of the Kent variant, several additional variants have been identified including the B.1.617.2 variant first identified in India, denoted 'Delta'. Data from 4-10 July 2021 showed that the Delta variant accounted for approximately 99% of sequenced cases in England;[74] and in Scotland, 97% of sequenced cases (data up to 28 May 2021).[75] Whilst evidence is still being amassed regarding variants, there is so far no indication that the transmission modes have changed and therefore no changes required to the current IPC measures.

Further information regarding the new variant(s) is provided in a separate ARHAI Scotland **rapid review.**

Conclusion:

- Transmission of SARS-CoV-2 is thought to occur mainly through close contact with an infectious individual, mediated by respiratory particles.
- Currently there is no clear evidence of 'traditional' long-range airborne transmission of SARS-CoV-2, however the contribution of air-mediated transmission, acknowledging a spectrum of droplet sizes, requires further research.

4.2 Clinical presentation

Whilst it is apparent that there is variation in the severity and range of symptoms experienced, the most frequently reported symptoms from case and cohort studies include fever and cough. [76-94] UK data also reflects this.[95, 96] Analysis of a large UK cohort of cases hospitalised between 6th February and 8th May 2020 (n=24,477) demonstrated that cough was the most prevalent symptom, followed by fever and dyspnoea.[97] Prevalence of individual symptoms varied with age, with fever being less marked at the extremes of age, and runny nose limited to mostly those aged <20 years, especially to those aged under 10 years. A core symptom set of fever, cough, and dyspnoea was identified, and accounted for the largest number of patients (n=9363, 36.%). This core symptom set was found to co-occur with additional symptoms in

three patterns; 1) fatigue and confusion, 2) diarrhoea and vomiting, and 3) productive cough. Similar symptom patterns were observed in 4,445 patients from a study of self-reported symptoms of mild disease.[97] Anosmia and ageusia (loss of smell and taste), although more subjective, have also been reported[76, 98-102] and these symptoms were added to the UK's official list of symptoms in May 2020. Amongst hospitalised paediatric and adolescent cases, the most frequently reported symptoms are also fever and cough.[103] This also appears to be the case in community cases, with runny nose also predominant, however the data is less reliable, being self-reported or reported by a family member.[104] Paediatric cases tend to have less severe disease, are hospitalised less frequently than adult patients and are less likely to be admitted to ICU.[105-113] Analysis of symptoms in 126 residents from 4 care homes in London found that early onset anorexia had the strongest independent association with a positive RT-PCR test; cough or shortness of breath were also significantly and independently associated, whilst fever, altered mental state, and diarrhoea were not.[114] More recently (July 2021) there have been anecdotal reports of milder illness with headache, runny nose, and sneezing common in self-report data from community cases,[115] however this has yet to be confirmed in published cohort studies and the extant UK official list of symptoms has not been updated. The effect of vaccination on symptom expression requires further research.

It is widely recognised that those individuals with underlying comorbidities (diabetes, cardiovascular disease, lung disease, cancer) have an increased risk of ICU admission and mortality.[116-124] [125] Analysis of 36,398 COVID-19 patients demonstrated that 42.5% had one or more pre-existing morbidity; the most common was hypertension (36.4%), cardiovascular disease (11.9%), and diabetes (22.0%) – mortality rate in the cohort was 14.5% (5,310/36,398).[119] Higher risk of death was associated with cardiovascular system diseases, immune and metabolic disorders, respiratory diseases, cerebrovascular system diseases, any types of cancer, renal and liver system diseases. Data from a UK cohort has shown that cardiovascular and cerebrovascular disease was significantly more common in patients that had died by 14 days (90% vs 48% in those still alive) and of these congestive cardiac failure was the most notably associated with non-survival (35% vs 11%).[95] Median age in this study was 75 years. Case fatality was 21%; the authors state this was much higher than that reported by other studies of all hospitalised patients; the age of the cohort was also higher. This was also the case at a South West London hospital in which case fatality was 32.6% in a 500 patient cohort; average age was 69 years (SD 19.23, range 1 week to 88 years).[126] It is widely recognised that older age groups have higher rates of underlying comorbidities and both have a correlation with a higher risk of COVID-19 mortality. Among paediatric cases, those with underlying comorbidities are significantly more likely to require hospitalisation and ICU

admission and have a higher mortality rate.[111, 127]

Analysis of 53,000 confirmed cases found that 7.7% experienced gastrointestinal symptoms, with approximately 5.7% experiencing diarrhoea.[128] The incidence of diarrhoea is more variable in smaller cohort studies (2-50%).[79, 81, 84, 95, 108, 118, 129-139 139] Nausea and vomiting are also infrequently reported (5.0% of 1099 confirmed cases from Mainland China).[136, 139, 140] The prevalence of diarrhoea/vomiting in addition to typical symptoms (fever, cough, dyspnoea) was estimated at 5.2% in a large UK cohort of hospitalised cases (n=25,477).[97] Patients reporting with gastrointestinal symptoms were more commonly female, had a longer duration of symptoms before presentation, and had lower 30-day mortality. In one cohort, (n=201) patients with gastrointestinal symptoms were reported as being younger and having less severe disease.[139] A number of early papers cited the need for more research into the possibility of faecal-oral transmission[2, 6, 7, 9-11, 113, 141] following the discovery of viral RNA in the stool samples of COVID-19 patients.[109, 142-149] Early studies reported on single patient cases[142, 143, 145, 150] and/or lacked robust clinical data[142, 144, 151] (i.e. time course of illness, incubation period) which limited interpretation of the epidemiological significance of clinical samples. Pooled detection rates of viral RNA in stool samples have been similar; 43.7% (191/436 cases),[152] 43% (934/2149),[153] and 46.5% (312/671).[154] Evidence has shown that viral RNA can be detected in stool in both children and adults after clearance in respiratory samples,[132, 136, 153, 155-157] in the absence of positive respiratory samples,[158] and following resolution of symptoms.[146, 147, 156, 159, 160] Viral RNA can also be detected in stool in the absence of GI symptoms.[161] The duration of PCR positivity of stool samples appears to be significantly longer than that of respiratory samples; median 19 days vs. 14 days respectively ($p<0.001$).[162] It is possible that the presence of viral RNA in stool is due to clearance from the mouth/throat into the gastrointestinal tract from swallowing. The transmission risk from non-respiratory samples is still being investigated. Initial attempts at live virus isolation from stool were unsuccessful,[163] however live virus has since been isolated from a stool sample taken approximately 19 days after symptom onset from a severe COVID-19 patient (who subsequently died) in China.[164] Following inoculation of Vero E6 cells, a cytopathic effect was observed after two days, and viral particles with the typical morphology of the SARS-CoV-2 virus was observed. Using inoculated Vero E6 cells, a cytopathic effect was also reported for 2/106 (1.9%) stool samples from 1/46 patients (2.2%) in France[165]. Both stool samples were from a 62-year-old immunocompromised male patient, collected 11 and 12 days' post GI symptom onset. Live virus has also been isolated from 62 stool samples collected from 23 patients using Vero cells; medium duration of shedding was 8 days post symptom onset and the probability of detecting isolated virus dropped below 5% after 15.2 days post symptom onset (95% confidence interval (CI) 13.4 – 17.2).[166] The sample

size in this preprint study was very small and further prospective studies that assess time course of viral shedding in stool in relation to illness progression in individual cases is required. Wolfel et al, in the absence of histopathology, analysed the presence of viral sgRNA in clinical samples, which is only transcribed in infected cells and therefore can indicate the presence of actively-infected cells.[163] They reported 'no or only minimal' indication of replication in stool by this method however this was a small study (n=9) and an area of research that requires further work. Limited data from endoscopic examination of infected patients has revealed positive staining of viral host receptor ACE2 in gastrointestinal epithelial cells, leading to the suggestion that gastrointestinal cells are actively infected[147] however this is a single study and an area of research that requires further investigation. To date there is no evidence of direct human-to-human transmission from faecal material.

It is worth noting that the application of standard infection control precautions (SICPs) would prevent ongoing transmission via the faecal-oral route.

Viral RNA has also been detected in blood samples from infected patients.[144, 148, 149, 167-173] However transmission risk via the blood would be expected to be very low and transmission via this route has not been previously reported for respiratory viruses.

A small cohort study describes identification of viral RNA in vaginal swabs in 2/35 women tested, however repeat testing was not conducted and there is the possibility of contamination from the perineum.[174] Three small cohort studies (n=10,[175] n=15,[176] and n=35[177]) failed to detect any viral RNA in vaginal fluid.[175-177] Follicular fluid aspirate of a single case was found to be PCR-negative.[178] Viral RNA has not been detected in testicular biopsy samples[179] or expressed prostatic secretion[180] in the small number of those tested although has been detected in semen both during infection and after symptom resolution.[181, 182] Semen samples from 34 Chinese males taken 1 month after COVID-19 diagnosis were all negative,[183] as was a sample taken 8 days post symptom onset from a single case with mild infection.[100] Semen samples from a cohort of 20 German males including 2 with active infection and 18 in the convalescent phase (8-54 days after absence of symptoms) all tested negative.[184] Samples from 6 males collected 1-3 weeks post symptom onset tested negative in the presence of positive saliva and nasal swabs.[185] Urine samples have tested positive in a small number of cases.[148, 169-171, 182, 186-188] From a meta-analysis of case series and cohorts with a sample size of ≥ 9, the estimated viral shedding frequency in urine was 1.18% (CI 95%:0.14 – 2.87).[189] Viral load in urine was low but detectable and cytopathic effects were observed 3 days after inoculation onto Vero E6 cells[186] but in a separate study, inoculation onto CaCo-2 cells did not yield results.[171] These findings do

not indicate infection of the kidneys or bladder however they do question the possibility of transmission via the urine.

Peritoneal fluid collected during emergency appendicectomy and caesarean section[190] tested negative for viral RNA.[191]

Post-mortem analysis has revealed presence of viral RNA in periodontal tissue.[192] Viral RNA was detected in 18.6% of dental biofilm samples collected from a small cohort of HCWs (n = 70).[193]

A study in a German hospital mortuary found that clinical samples from nasopharyngeal and various body site swabs of deceased COVID-19 patients have tested positive for viral RNA up to 9 days post-mortem (>1,000 copies per mL) but were not found to be viable in Vero cells.[194]

Post-mortem analysis of various samples (nasal, lung, throat swabs) identified presence of SARS-CoV-2 at 128 hours (tracheal swab)[195] and 120 hours post-mortem (nasal, lung)[196] Viability of SARS-CoV-2 was not assessed in these studies.[195, 196] All endobronchial swabs taken during autopsy carried out between 1 and 6 days post-mortem were positive for SARS-CoV-2 using RT-PCR testing; one lung sample taken 6 days post-mortem demonstrated viable SARS-CoV-2 via viral culture.[197] A study performed in Germany also demonstrated viable SARS-CoV-2 in oropharynx, trachea and lung swab samples taken 4-days post-mortem in one case; and peri-oral, trachea and lung swabs taken 17 days post-mortem.[198]

SARS-CoV-2 has been detected in the tears and conjunctival secretions in COVID-19 patients with conjunctivitis[4, 199-205] and without,[202-204, 206-210] leading to the suggestion that transmission could be possible via the mucous membranes and secretions of the eyes.[211, 212] A positive culture sample grown from an eye swab in Vero E6 cells has been reported.[205] Conversely, a cohort (n=39) that had conjunctival samples consecutively tested reported negative PCR results in all samples.[213] As sampling of the eyes is not routinely carried out, the overall proportion of cases that have positive eye secretions is unknown. A systematic literature review may yield more robust evidence. Presently there is no clear evidence of ocular transmission; further information regarding ocular transmission has been covered in the **eye protection rapid review**.

All secretions and excretions from patients with known or suspected COVID-19, should be regarded as potentially infectious.

There is limited evidence regarding mother-to-child transmission. The majority of studies describe development of COVID-19 in the third trimester with subsequent caesarean deliveries and no evidence of vertical transmission.[214 215-235] There is less evidence for vaginal births but

the majority have reported no evidence of vertical transmission. [215, 224, 226, 230, 234-250] Seven rapid systematic reviews found no clear evidence of vertical transmission,[239, 251-257] however a systematic review reported a pooled rate of 3.2% (95% CI; 2.2-4.3%) for possible vertical transmission (27/936 neonates tested positive via RT-PCR within 48 hrs of birth).[258] The World Health Organization in February 2021 provided a definition for determining a confirmed vertical (in-utero) transmission case, requiring a positive neonatal PCR test up to 48hrs post birth as well as a positive sterile sample (e.g. amniotic fluid, neonatal blood) at age <24 hrs.[259] Eight neonates have tested positive by RT-PCT within 24 hrs of birth (2 caesarean, 6 vaginal) with additional positive obstetric tissue samples (amniotic fluid, placenta, umbilical stump); four neonates developed fever at birth, four remained asymptomatic.[260-266] The mother of one of the neonates was symptomatic at delivery but tested negative by RT-PCR, showing positive serology 10 days later.[262] Thirty two reports describe positive neonatal samples in 49 neonates within 36 hrs of birth but obstetric samples were either not collected/tested[267-295] or tested negative.[217, 296-299] In these studies, the majority of neonates (33/49; 2 unreported) were delivered by caesarean section; twenty-nine mothers had mild infection, 2 asymptomatic, 4 severe, and 13 unreported, and all were in the late 2nd or 3rd trimester, except two who were preterm (29 weeks). A single neonate born at 34 weeks via caesarean section tested positive at 49 hrs of life with positive cord blood and urine but remained asymptomatic.[300] Placental/membrane samples have also tested positive and displayed positive histopathology but in the absence of positive neonatal RT-PCR results.[241, 301-303] Five cases of spontaneous abortion were associated with presence of SARS-CoV-2 in placental tissue following maternal infection in the first[304, 305] and second trimesters.[306-308] In contrast, this was not the case in a cohort of 24 1st and 2nd trimester spontaneous abortions.[309] Further research is required out-with this rapid review. Antibody testing conducted in neonates has demonstrated mixed results; positive IgM and IgG tests in a number of cases,[310] positive IgG and negative IgM in one case,[311] however in one neonate born to a mother with severe infection, both neonatal IgM and IgG tests were negative.[268] Amongst a cohort of 11 infants born to mothers with COVID-19, all had detectable IgG (100%) and 5 (45.5%) had detectable IgM at birth; RT-PCR test results were all negative.[312] The majority of studies which have tested obstetric samples have not been able to detect viral RNA in amniotic fluid, cord blood, placenta, or breast milk in those tested.[237, 238, 248, 251, 252, 254, 292, 313-321] A systematic literature review (included studies published up to Oct 2020) reported an overall pooled proportion for SARS-CoV-2 RNA detected in breast milk of 2.16% (95%CI: 0.0-8.81%).[322] A small number of cases have reported positive breast milk. RT-PCR testing from a sample taken 1 day after delivery was positive however repeat sampling 2 days later was negative.[323] In a separate case, samples taken 10 days post birth were positive but subsequent tests on days 14-25 were negative.[324] A third case describes positive viral

samples from breast milk of an asymptomatic mother, ingested by a neonate that became SARS-CoV-2 positive at 9h hrs post-vaginal delivery, however alternative transmission routes could not be ruled out.[325] Findings from a larger study detected SARS-CoV-2 RNA in the milk samples of 7 (10.6%) out of 66 women with PCR-confirmed infection however viral RNA was not detected via RT-PCR in subsequent tests on days ranging from 1 to 97 days later.[326] There was no clinical evidence of transmission from these women to their breastfed neonates.[326] One study was unable to detect replication-competent virus in breast milk samples, however these originated from one woman only.[327] Transmission events from breast milk to neonate have not been demonstrated to date.[328-330] The WHO recommend that mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breastfeed.[331] One neonate delivered vaginally in Italy developed symptoms and tested positive 3 days after birth but it is not clear if the baby was isolated from the mother after birth.[332] Whilst many studies describe IPC and isolation measures put in place during and following birth, it is possible that COVID-19 may have been transmitted to neonates from routes other than vertical; immediate testing on delivery may provide more clarity. Overall, evidence suggests very low risk of vertical transmission.

Conclusion:

- The most frequently reported symptoms associated with SARS-CoV-2 infection are cough and fever; anosmia and ageusia (loss of smell and taste) are also frequently reported.
- The incidence of diarrhoea and vomiting during SARS-CoV-2 infection is variable (5-50%).
- The risk of vertical transmission in pregnant women is very low.
- All secretions and excretions from suspected/confirmed infectious individuals should be treated as potentially infectious.

4.3 Atypical presentations

Atypical presentations include cases that do not display the typical clinical symptoms (fever, cough) (which constituted the case definition to date) but may test positive or show radiographic abnormalities (i.e. ground-glass opacity). The absence of respiratory symptoms/fever has frequently been reported in neonates/children[87, 105, 110, 112, 167, 333-336] and less so in adults[80, 133, 337], with diagnosis often relying on RT-PCR and radiological investigation. From analysis of UK

cases (n=24,477), those presenting with confusion in the absence of any other symptoms tended to be older (82 years, IQR 75-88).[97] The association between advanced age and confusion was mirrored by a higher prevalence of dementia in these groups. Conjunctivitis in the absence of any other symptoms has also been reported.[201, 338] An atypical presentation occurred in an Italian national evacuated from China and quarantined on arrival with 56 others as a precautionary measure.[150] This case was a healthy 28 year old male who had no respiratory symptoms but had mild conjunctivitis and slight tonsillar exudate in the presence of positive naso- and oro-pharyngeal samples and stool samples.

A rare Kawasaki-like disease has been identified in a small number of children presenting with COVID-19 in multiple countries.[339-341] Presence of body and acral rashes with or without additional symptoms has been reported.[342] Hormati et al provide a brief report on the admission of two patients to a gastroenterology clinic in Iran with unusual gastrointestinal symptoms; both tested positive for COVID-19 in the absence of respiratory symptoms or fever.[343] Again, no transmission events were reported from these patients. A case report describes possible transmission from a 94 year old patient with atypical presentation (delirium, abdominal pain).[344] Nine HCWs and another inpatient developed COVID-19 after the patient was treated in three wards over 5 days with no infection control precautions, highlighting that there is risk of transmission from atypical presentations where no precautions are taken. From UK data, identification of four symptom patterns (gastro-intestinal symptoms, productive cough, confusion, and pauci-symptomatic presentations) were identified as usefully distinct in terms of clinical utility for identifying atypical presentations.[97] Based on the increasing number of reports of atypical presentation, it may be pragmatic to consider widening the case definition as more evidence arises.

Conclusion:

- Atypical presentations include any symptoms that deviate from, or present in the absence of, the 'classic' range of COVID-19 symptoms and may include the following: conjunctivitis, abdominal pain, confusion and delirium, as well as a rare Kawasaki-like disease in children.

4.4 Asymptomatic transmission

A study by Ma et al (*not peer-reviewed*) that assessed clinical symptoms reported by 7 countries, calculated that, among RT-PCR-positive cases with relevant information (n=329), 49 (15%) were asymptomatic however it was not stated if radiographic symptoms were

present.[78] Studies have also reported positive asymptomatic cases, identified during contact tracing, that remained asymptomatic up until the point of negative RT-PCR conversion[345-347] or for the duration of a specified follow-up period.[348-352] Universal screening of 52 asymptomatic obstetric patients in Japan identified low prevalence of infection in the cohort (3.8%); all cases remained asymptomatic.[353] A systematic literature review reported an asymptomatic-positive prevalence of 20% (95% CI, 17%-25%, n=6,832) with individuals remaining asymptomatic throughout the course of infection.[354] Data suggested that the risk of transmission from asymptomatic individuals may be lower than that of symptomatic individuals, however further research is required. Risk of bias from these studies was high, in part due to selection bias. To date, there has been limited evidence of transmission from positive-asymptomatic cases, however this may be due to the challenge in identifying such index cases. Contact tracing of a Chinese cohort identified 8 clusters with evidence of asymptomatic transmission from 11 asymptomatic infectees.[349] A number of studies report on identification of viral RNA in clinical samples in asymptomatic patients,[159, 167, 348, 355-359] and contact tracing has identified possible transmission from a small number of these cases.[99, 350, 357, 360] Further, nasopharyngeal swabs from a small proportion of asymptomatic individuals have been shown to exhibit cytopathic effects upon Vero E6 cells in culture.[359] Additionally, saliva samples showed positive replication of viral culture in Vero E6 cells in two asymptomatic/pre-symptomatic individuals.[361] Contact tracing identified a possible asymptomatic index case in a family cluster in China[357] and in Vietnam;[99] both cases had normal CT imaging and no symptoms. Possible asymptomatic transmission was documented on a flight from Italy to South Korea. All passengers were quarantined on arrival at a government facility for 14 days; 6 passengers tested asymptomatic-positive on the first day of quarantine; one passenger developed symptoms on day 8 of quarantine and tested positive, likely having acquired infection from one of the asymptomatic-positive passengers.[350] A systematic literature review that assessed studies up to July 2020 reported a secondary attack rate estimate of 1% (95% CI: 0%-2%) from asymptomatic cases, however the prediction interval ranged from 1-10%.[362] This was in comparison to 6% (95% CI: 5%-8%) for symptomatic index cases.

There may be an association between asymptomatic presentation and younger age.[363] A growing number of paediatric cases have been reported detailing asymptomatic presentations with positive clinical samples however transmission events from these cases could not be proven.[87, 104, 106, 110, 159, 167, 346, 355, 364-366] Assessment of a Korean cohort (n=91) of children <19 yrs old found that 42% were asymptomatic at the time of PCR diagnosis and remained so at follow-up.[367] The proportions of asymptomatic-positive cases are difficult to contextualise due to a lack of point-prevalence-type data from asymptomatic individuals in the wider

community. Data from asymptomatic testing of HCWs has revealed a small proportion to be asymptomatic-positive however transmission events from these individuals was not reported. A point prevalence study of US HCWs at a single centre in New York identified 4.1% (4/98) to be asymptomatic-positive at testing, 2 remained asymptomatic at follow-up.[368] A point prevalence study of UK HCWs undertaken in April found that 2.4% (13/545) were asymptomatic-positive at testing and 8 remained so at follow-up.[369] A smaller UK study that routinely tested a cohort of asymptomatic HCWs on a weekly basis identified 44/400 (11%) that tested positive in the absence of symptoms in the week before or after positivity.[370] Results from the study suggest a likely reflection of general community transmission, however it does raise concern about the risk of transmission from these individuals. Asymptomatic-positive residents have been identified during universal outbreak screening at long term nursing facilities in the US.[371, 372] Up to 10.3% (13/126) were asymptomatic-positive during an outbreak and remained so over a 30 day follow up, but symptom history pre-testing was not obtained.[371] It is essential that follow-up is undertaken to determine if cases remained asymptomatic-positive or were actually pre-symptomatic, and whether any transmission events from these individuals occurred.

Conclusion:

- There is evidence of asymptomatic transmission of COVID-19 however the overall prevalence of this in the population at any one time remains unknown.
- Standard Infection Control Precautions (SICPs) should always be applied in all situations regardless of the infectious nature of the patient.
- All persons should adhere to the requirements for physical distancing and extended use of face coverings whilst in health and care settings.

4.5 Pre-symptomatic transmission

Possible transmission in the incubation period has been reported in a number of studies, mainly small cluster case reports.[356, 373-383] A recent report detailed possible pre-symptomatic transmission in 7 community case clusters in Singapore; date of exposure could be determined in 4 clusters which suggested transmission occurring 1-3 days prior to symptom onset from source patients.[374] Analysis of 72 infector-infectee pairs in South Korea estimated transmission onset to have occurred 0.72 days prior to symptom onset; pre-symptomatic transmission was estimated to be applicable to 37% of cases.[381] Data from a large Chinese cohort (n=1178)

estimated infectiousness to have peaked 1.8 days before symptom onset, with the proportion of pre-symptomatic transmission estimated at 62.5% from 43 transmission events recorded in 23 clusters.[349]

Rothe et al report a single case of a Chinese national that travelled to Germany for business and reported hearing coughing from the rows behind on the airplane but was asymptomatic for the duration of contact with German colleagues.[356] Having developed symptoms on return to China, contact tracing was carried out and two German colleagues were identified as positive with mild symptoms. A cluster of cases in Germany developed from this travel-related cluster and a further pre-symptomatic transmission event was identified between 2 individuals that met in a work canteen; this transmission event was strongly supported by virus sequence analysis.[378]

Contact during the incubation period during a conference was identified as a possible mode of transmission from a single person to 2 family clusters in China; symptoms in the index case developed 2 days after the conference.[375] Transmission in a cluster of young people (16-23 yr olds) in China was linked to an asymptomatic index case who had contact with all persons in the cluster; all cases including the index case subsequently developed symptoms.[376] The estimated incubation period was notably short (median 2 days) in this study. Two further cases of pre-symptomatic transmission were implicated in familial clusters in China; both cases had contact with a pre-symptomatic individual from Wuhan.[375] Contract tracing studies from China have also described possible pre-symptomatic transmission in the incubation period in clusters of community cases.[377, 384] As with the aforementioned studies, there were no severe or critical patients in this cohort. Analysis of an outbreak aboard an aircraft carrier identified 30.5% of those that tested positive to be pre-symptomatic at the time of testing; transmission from these individuals cannot be ruled out due to the close proximity living and working conditions in the cohort.[351]

It is notable that the majority of these studies did not have clinical data available in the incubation period and relied on contact tracing analysis and retrospective data collection, which is prone to recall bias. There is also the possibility of unidentified infectors in these studies. A more robust evidence base is dependent on widespread clinical sampling from mild/community-based cases (and asymptomatic individuals).

Conclusion:

- There is limited evidence of pre-symptomatic transmission of COVID-19 and the overall prevalence of this in the population at any one time remains unknown.

- Standard Infection Control Precautions (SICPs) should always be applied in all situations regardless of the infectious nature of the patient.

- All persons should adhere to the requirements for physical distancing and extended use of face coverings whilst in health and care settings.

4.6 Nosocomial transmission

Data regarding symptoms in HCWs confirms a mirroring of symptoms experienced by the community/general population.[385] In a Dutch cohort of 86 COVID-19-positive HCWs, the majority suffered relatively mild disease and 93% met a case definition of fever and/or coughing and/or shortness of breath.[386] Other symptoms included headache, runny nose, sore throat, chest pain, and diarrhoea. A large proportion (63%) of those screened worked whilst being symptomatic, therefore the possibility of HCW-HCW and HCW-patient transmission (or indeed community transmission) cannot be ruled out, especially considering only 3% reported exposure to a positive inpatient.

There are published reports of clear nosocomial transmission during the earlier stages of the epidemic both in the UK and abroad.[387-389] In Glasgow, nosocomial infection was documented in patients admitted to medicine for the elderly wards across three hospital sites; 103 patients tested positive after 14 days of admission.[389] Mean age of the cohort was 82 years however the infections were recorded prior to the roll out of the Scottish over 70's testing policy (with repeat testing at day 5) on 29th April 2020; had this been in place, infections would very likely have been identified earlier, as atypical presentation and dementia were challenges for diagnosis in this cohort. Reports from a South West London hospital revealed that 51 of 500 analysed admissions developed COVID-19 nosocomially whilst inpatients.[126] A separate inpatient cohort (n=435) from a London teaching hospital reported that 47 cases over a 6 week period met the definition for definite hospital acquisition (symptom onset 14 days or more after admission); many of these cases were identified as having been in the same bay or ward as a patient with PCR-confirmed COVID-19.[390] Analysis of cases admitted between 1st March and 19th April 2020 at a south-east London teaching hospital revealed that 7.1% (58 cases) were classed as hospital-associated; median time from admission to symptom onset was 32.5 days (IQR 21-65).[391] Nosocomial transmission from an unknown individual to a patient in an ITU, with subsequent transmission to 5 patients and 16 HCWs within the ward, occurred at a tertiary care university hospital in the UK. The infection cluster occurred after hospital visits were stopped and at the same time as lockdown was announced.[392] A lack of social distancing

between staff may have contributed to transmission, as the working environment did not allow adequate spacing; unfortunately WGS was not carried out in this study therefore it was not possible to analyse the transmission events with greater clarity. An outbreak on the paediatric dialysis unit of a German hospital involved transmission from an index patient to 7 HCWs and 3 patients.[393] Transmission from an undiagnosed neurosurgery patient to 12 HCWs occurred at a hospital in Wuhan; appropriate PPE was not worn, with many HCWs not wearing surgical masks.[394] Possible transmission from an undiagnosed patient to 3 HCWs was suspected to have occurred when performing a bronchoscopy ('procedure' masks were worn, not respirators), however genetic sequencing was not carried out and contact tracing is not described in detail.[395] A case report describes possible transmission from a 94 year old patient with atypical presentation (delirium, abdominal pain) to 9 HCWs and another inpatient after the patient was treated in three wards over 5 days with no infection control precautions.[344] The differing case definitions used by various studies to define hospital-associated COVID-19 make direct comparisons challenging.

Research conducted in March/April 2020 with NHS England Trusts to inform the Scientific Advisory Group for Emergencies (SAGE) suggested that nosocomial transmission of COVID-19 was occurring during that time, with 8.2% of cases being diagnosed 14 days post-admission (inter-quartile range 3.8% to 12.0%). It was reported that few Trusts were assessing the possible involvement of HCWs in transmissions – notably, this was prior to the introduction of universal mask wearing.

As sustained community transmission has occurred as the pandemic has progressed, it has become more challenging to identify true nosocomial transmission events particularly in regards to HCW acquisition. In Scotland, during the period 1st March-6th June 2020, HCWs or their households made up 17.2% (360/2097) of all hospital admissions for COVID-19 in the working age population.[396] Healthcare workers in patient-facing roles were at higher risk of hospital admission (hazard ratio 3.30, 2.13-5.13) than non-patient-facing HCWs, as were their household members (1.79, 1.10-2.91).[396] Most patient facing HCWs were in "front door" roles (e.g. paramedics, acute receiving specialties, intensive care, respiratory medicine). Those in non-patient-facing roles had a similar risk of hospital admission as the general population. This was not the case in an English cohort; screening of 1654 symptomatic HCWs by an English NHS Trust between March 10-31st 2020 identified 240 (14%) positive individuals; comparison of rates between staff in patient-facing and non-patient facing roles found no evidence of a difference, suggesting that data may reflect wider patterns of community transmission rather than nosocomial-only transmission.[397] Mirroring of community transmission was also identified at a large public hospital in Madrid,[398] and at three hospitals in the Netherlands; contacts with

COVID-19 individuals was reported from out-with the hospital and from contact with colleagues.[399] Complete genome sequencing of 50 HCW and 18 patients suggested that the observed patterns were most consistent with multiple introductions into the hospital.[399] Genetic sequencing provided confirmatory evidence for community transmission to a HCW, ruling out suspected transmission from two COVID-19 patients.[400] Whole genome sequencing was used as part of outbreak investigations at a hospital in Ireland and revealed that HCWs moving between wards were responsible for transmission to patients and other HCWs.[401] Transmission between surgical staff at a hospital in Florida, US, was identified prior to the introduction of universal masking in the facility; surgical staff at the time were wearing N95 respirators when treating suspected/confirmed COVID-19 patients; this highlights the risk of transmission potentially not linked to provision of care.[402] Sharing of patient transport was implicated in facilitating patient-patient transmission between renal dialysis patients, where WGS assisted identification of the cluster.[403] In a Portuguese hospital, WGS also assisted identification of both HCW to patient and HCW to HCW transmission on a non-COVID-19 ward.[404] Although WGS can help in identifying nosocomial clusters, it is often impossible to determine the source and subsequent direction of transmission.[405] This is especially the case where there is limited data on the genetic background of strains circulating in the community, and incomplete genetic analysis of nosocomial cases. In March 2021, the UK Scientific Advisory Group for Emergencies (SAGE) stated that evidence shows there is variation in both nosocomial infection rates and HCW infection rates, which cannot be explained by levels of respiratory protection alone, with key drivers of nosocomial infection being the community infection rate and hospital occupancy.[406]

Whilst transmission from asymptomatic HCWs has not been documented, a UK study identified a small proportion (0.5% of 1,032) of asymptomatic-positive HCWs during a routine screening study in April 2020, highlighting the risk of transmission from these individuals.[407] HCWs working in ‘red’ or ‘amber’ wards were significantly more likely to test positive than those working in ‘green’ wards (p=0·0042) – this was the case for both symptomatic and asymptomatic-positive HCWs. Contact tracing at a hospital in the US that involved testing of asymptomatic HCWs revealed a number of exposures between staff to have occurred when the index HCW case was pre-symptomatic.[408] None of the confirmed HCW cases occurred in staff working on COVID-19 designated wards; exposure on non-COVID-19 wards was attributable to delayed diagnosis which was reduced as availability of testing and awareness of atypical presentations increased, and as routine admission screening was implemented. The authors proposed that some of the transmission to HCWs might have been attributable to non-compliance with facemask use in nonclinical shared work areas (e.g. nursing station, staff

work, or break rooms) or during activities such as meals when facemasks were removed, and social distancing was not maintained. Data from 4 London care homes identified 44 residents (17% of the 264 cohort) that were asymptomatic-positive and remained so at follow-up.[114] Further, 7.9% were pre-symptomatic.[409] Some SARS-CoV-2 sequence variants were highly similar between residents and/or staff within a single care home; there were also multiple distinct clusters of SARS-CoV-2 sequence types within single nursing homes, suggestive of multiple introductions.[114] Analysis of 24 Irish care homes found the median proportion of asymptomatic-positive staff was 19.6% (IQR 11.8-52.3%); asymptomatic was defined as without symptoms 7-days either side of a test.[410] Over 25% of residents with lab-confirmed infection were asymptomatic. It was not possible to determine the impact of these individuals on transmission in these settings.

In Scottish acute settings, unpublished outbreak reporting has highlighted the contribution of both HCWs and patients to nosocomial transmission (and visitors to a lesser degree).
A number of recurring themes have emerged when considering factors likely to contribute to transmission. Non-clinical HCW activities include car-sharing, socialising outside of work, and shared break times. Patient risk was linked to inpatients not wearing face coverings, patients moving around clinical areas, and patients being transferred between wards prior to a PCR result. Poor compliance with mask wearing (in HCWs and visitors) and physical distancing as well as HCWs working whilst symptomatic were also identified. A report published by the Healthcare Safety Investigation Branch concluded that more should be done with regards to the design of ward work systems and equipment layout to mitigate the risk of nosocomial transmission.[411] In particular, the investigation observed limited mitigation strategies in the design of the physical environment, and in staff work patterns, to enable staff to take breaks in environments whilst maintaining physical distancing. Typically, due to limited time available to take a break, staff would need to use small rooms adjacent to their clinical environment, with a lack of opportunities to increase levels of ventilation. Although the investigation involved NHS England trusts, there are similarities in the built environment and nursing cultures in Scotland, and these issues are likely experienced in other countries too. At a German hospital, removal of masks during staff breaks was identified as a potential contributor to transmission between staff,[412] this was also noted as a risk factor in an Indian cohort.[413] In a French HCW cohort (n=99), not wearing facemasks during staff meetings was associated with risk of infection.[414] Poor mask compliance in visitors was also noted during an outbreak involving patients and visitors/guardians in a haematology ward in South Korea.[415] Expert opinion has also identified the difficulties in maintaining adherence to physical distancing, particularly in older builds with nightingale wards, highlighting that a whole systems approach should be implemented to

mitigate human nature/behaviour and support adherence.[416] Looking at non-acute settings, a study of Canadian care homes indicated that overcrowding was associated with higher incidence of infection and mortality, indicating that inability to isolate residents may have facilitated transmission.[417]

With regards to the risk of transmission from visitors, there is a lack of clear evidence in the literature. Visitors have been implicated as potential sources of transmission in Scottish acute settings in a small number of incidents (unpublished) however the nature of retrospective investigation coupled with the complexities of contact tracing during a global pandemic prevents confirmation of the precise transmission routes. Visitors are also at risk of acquiring COVID-19 whilst visiting healthcare facilitates and anecdotally this has occurred in Scotland. Whilst the aim from an infection prevention and control perspective is to reduce the infection risk, consideration must be given to the unintended negative effects on patients and families where visiting is restricted. This is particularly an issue in situations involving critical care and end of life care. The Scottish Government has produced guidance to support the safe reintroduction of visitors into hospital settings,[418] the specifics regarding requirements for visitors is outlined in the NIPCM COVID-19 addendum.[419]

It is notable that not all unprotected exposures to COVID-19-positive individuals result in transmission, even when being exposed to AGPs without respiratory protection.[65] None of the 21 HCWs that reported contact with an undiagnosed patient with mild respiratory symptoms at a Swiss hospital tested positive when tested 7 days later.[420] The patient underwent routine clinical examinations, blood draws, electrocardiograms, chest X-rays and had nasopharyngeal swabs taken; masks were never worn by HCWs during the patient's care. In Germany, a physician worked over a number of days in a hospital whilst symptomatic (coughing, fever) and with no mask, but did not transmit infection to any of the 254 identified contacts (HCWs and patients).[421] In Singapore, 41 HCWs were exposed to multiple AGPs at a distance of less than 2 metres for at least 10 minutes while wearing predominantly surgical masks (only 25% wore N95 respirators) whilst caring for a patient with undiagnosed COVID-19; none of the HCWs developed symptoms or tested positive (with repeat testing) in the 14 days following exposure.[422] Exposure to 5 patients with atypical presentations at a hospital in Singapore was not associated with subsequent infection in HCWs; the majority were wearing surgical masks at the time; the potential impact of varying viral load in these patients was not investigated.[423] This highlights the role of multiple factors in transmission.

Conclusion:

- Standard Infection Control Precautions (SICPs) should always be applied in all situations regardless of the infectious nature of the patient.
- Droplet precautions should be implemented when in close contact (within 2 metres), or providing direct patient care to a suspected/confirmed COVID-19 patient.
- Airborne precautions should be implemented when undertaking an AGP on a suspected/confirmed COVID-19 patient within the medium risk (amber) and high risk (red) pathways (optional for AGPs in the low risk (green) pathway).
- Visitors should be managed according to the NIPCM COVID-19 addendum.
- When not providing patient care, HCWs should continue to adhere to the pandemic controls (physical distancing, extended mask wearing) as outlined in the NIPCM COVID-19 addendums.

4.7 Reinfection

There have been a small number of published articles detailing individuals (n=13) having two distinct COVID-19 illnesses caused by genetically distinct SARS-CoV-2 strains.[424-433] Two of these cases were asymptomatic in both episodes of infection.[429] One case was re-infected with the new UK strain VOC-202012/01 of lineage B.1.1.7.[430] The time period from PCR-positivity in the first to the second infection episode ranged from 48 days to ~8 months. None of these cases were associated with onward transmission. The UK SIREN study reported 47 cases of potential reinfection in HCWs based on an initial PCR positive test followed by a subsequent PCR positive test a minimum of 90 days later; however, genomic analysis was not undertaken to confirm whether the infections were genetically distinct.[434] The median interval between the first PCR positive date and the potential reinfection PCR positive date was 162 days (95-223). Details regarding symptoms related to the second PCR test were not provided. In a recent surveillance report published 17th June 2021, Public Health England identified 15,893 possible reinfections (based on 2 sequential PCR or lateral flow device positive test ≥ 90 days apart) in England of which 53 were confirmed by sequencing as genetically distinct specimens from each illness episode.[435] There is so far nothing to indicate that a change in IPC measures is required to manage these types of cases. The ECDC recommend that a case definition for reinfection should include laboratory confirmation of two infections by two different strains but that the

minimum genetic distance and the minimum time period between illnesses is still to be determined/supported by phylogenetic and epidemiological data.[436] In a technical report published 8 April 2021, the ECDC[437] proposed a standardised surveillance case definition for suspected SARS-CoV-2 reinfection taking into account the emerging variants of concern (VOCs) with immune escape potential. A *suspected* COVID-19 reinfection case is defined as: "Positive PCR or rapid antigen test (RAT) sample ≥ 60 days following: a previous positive PCR; previous positive RAT; and previous positive serology (anti-spike IgG Ab)".[437] The Pan American Health Organization in collaboration with the WHO advise that a confirmed case should be determined by complete genomic sequencing for both the primary infection sample and secondary infection sample to confirm they belong to different genetic clades or lineages, regardless of the number of single nucleotide variations (SNV), stating that the virus is expected to mutate by approximately two SNVs per month.[438]

In regards to routine testing of recovered healthcare workers, Scottish guidance advises that social, community and residential care staff who have previously tested positive by PCR are exempt from being retested for a period of 90 days from their initial illness onset, unless they develop new symptoms.[439] This is to account for possible prolonged shedding and based on the assumption of immunity in the immediate term following infection. Scottish Government guidance for acute care staff (those working in oncology, elderly care and mental health wards, with stays over three months) states that a return to weekly PCR testing is not recommended following a positive result, only if symptoms reappear should staff be tested again, however do not advise when PCR testing should recommence.[440] However, it is advised that staff who tested positive from a PCR test are exempt from commencing/recommencing *lateral flow testing* for a period of 90 days after their PCR positive test was taken. Voluntary twice-weekly lateral flow testing for asymptomatic HCWs was introduced in December 2020.[441] From the reinfection cases identified to date, it would appear that immunity is either not induced and/or not protective against different strains; follow-up and analysis of larger COVID-19 cohorts (and ideally asymptomatic HCW testing cohorts) will provide valuable information on this topic. The ECDC report there are no studies designed to assess risk of transmission from reinfection, but that cohort studies to date estimate some protective effect up to five to seven months, which is lower in individuals aged 65 years and older, and does not apply to emergence of variants of concern.[442]

With the vaccine rollout, there is heightened interest in reinfection. Vaccine effectiveness is out with the scope of this rapid review.

Conclusion:

- All persons, including those who have recovered from COVID-19 infection and those who have been vaccinated, should continue adhering to the IPC measures currently in place to mitigate the risk of COVID-19 transmission.

4.8 Incubation period

Many of the studies published to date are limited by small sample sizes and over-representation of severe cases, the incubation period for which may differ from that of mild cases. Evidence suggests an incubation period of 5-6.3 days[7, 10, 88, 118, 135, 378, 382, 385, 443-463] with a range of 1-14 days[7, 8, 11, 81, 84, 118, 140, 381, 385, 446, 447, 449, 450, 460, 463-468] from infection to symptoms surfacing. Analysis of 2,555 Chinese community cases indicated a longer incubation period of 9 days.[469] Lauer et al estimate that most (97%) of those who develop symptoms do so within 11.5 days of infection (95% CI, 8.2-15.6).[445] Analysis of a small Chinese cohort (n=183) provided an estimate that 95% of those who develop symptoms will do so within 14 days of infection (95% CI; 12.2-15.9).[470] Consequently only a limited number of cases will potentially develop symptoms out-with the 14 days of self-isolation that is required following contact with a confirmed case. Analysis of viral load in a Spanish cohort found that time to symptom onset decreased in a dose-dependent manner as viral load at baseline increased.[471] A change to the isolation period required for contacts from 14 to 10 days was announced by the UK Chief Medical Officers which came into effect from 14th December 2020.[472]

Conclusion:

- The incubation period for most individuals is reported as 5-6.3 days (range 1-14 days).
- Self-isolation for 10 days is recommended for contacts of symptomatic cases.

4.9 Infectious period

In most cases, individuals are usually considered infectious whilst they have respiratory symptoms; how infectious an individual is likely depends on the severity of their symptoms and stage of their illness. Initial data from Wuhan suggested a median time from symptom onset to clinical recovery for mild cases of approximately 2 weeks, and 3-6 weeks for severe or critical cases however this data is likely biased by the fact that the majority of cases included in the study were hospitalised; the proportion of milder community cases is likely underestimated.[446]

Less is known about the duration of infectivity. From limited international data, the balance of evidence is that, for mild cases of infection, infectivity (as determined by respiratory RT-PCR sampling) peaks at symptom onset and significantly reduces 7 days after the onset of symptoms but appears to take longer for severe cases.[163, 446, 473-479] This peak in viral RNA was observed in a multi-centre study in Canada which recruited 2 mild community cases and 73 hospital inpatients; average viral load decreased approximately 10-fold over a period of 7 days, where average viral load was approximately 104.0 PFU/mL on the hypothetical day 0 of infection.[480] Community transmission on the day of symptom onset (when symptoms are mild and non-specific) has been reported but is reliant on retrospective self-reported data.[480, 481] Analysis of 301 hospitalised cases revealed that the positive rate of RT-PCR assay was highest at day 0−7 (97.9 %) after symptom onset then decreased with time; after 4 weeks, 26.3% of samples were still positive.[482] It was also observed that patients ≥65 years old shed virus for a longer period (22 days vs 19 days, p=0.015). A further cohort (n=1023) of mainly hospitalised patients demonstrated the positive rate of RT-PCR in nasopharyngeal samples to be highest (89% (95% CI 83-93) between 0 and 4 days post-symptom onset, dropping to 54% after 10-14 days.[483] Limited data in children has shown viral load peaking at day 2-3 after symptom onset.[484] Overall, the evidence base suggests that viral load likely peaks at or immediately following symptom onset.

Prolonged detection of viral RNA in respiratory and stool samples for up to 28 days (and in some cases up to several months) after symptom onset has been reported from hospitalised and community cohorts.[102, 484-497] Being immunocompromised may also be associated with prolonged PCR detection.[498-503] Analysis of a US cohort of 121 patients and HCWs demonstrated an average time of 24 days after symptom onset for transition from RT-PCR positive to negative; 10% remained positive 33 days after symptom onset.[504] Details of symptoms and infection severity were not reported, however there is evidence that patients with severe infection (requiring ICU admission) shed virus (as detected in nasal swabs) for significantly longer than non-ICU patients.[207, 477, 478, 493] In a meta-analysis (n=1235; 345 severe/critical, 890 non-severe) adults with severe/critical COVID-19 illness had persistent lower respiratory tract (LRT) viral shedding between 4-10 days after symptom onset with no significant trend in viral clearance (p=0.105) whereas non-severe cases had rapid clearance from the LRT at -0.41 (95%CI: -0.64 – 0.19; p<0.001) $\log_{10}$ copies/ml day^{-1} with an estimated mean duration of shedding of 20.4 days (95%CI: 13.2 - 27.7) after symptom onset.[479] In one cohort study (n=76, 30 severe, 46 mild), 90% of mild cases were PCR-negative by 10 days post-onset, while all the severe cases were still positive at 10 days post-onset.[477] In an Italian community cohort, viral clearance was achieved by 60.6% (704/1162) of patients, with a median

of 30 days from diagnosis (IQR 23-40) and 36 days from symptom onset (IQR 28-45).[505] From a retrospective cohort of 537 symptomatic community cases in Germany (isolating at home), 53.5% remained positive by PCR at 14 days after symptom onset.[506] A mean duration of viral RNA detection was estimated at 14.96 days after symptom onset. Hospitalisation before home isolation was associated with a 26% longer duration of PCR positivity compared with patients in home isolation throughout (time ratio: 1.26; p=0.049). Details regarding the presence and severity of symptoms throughout the isolation period were not provided. In a small retrospective cohort of patients (n = 206) admitted to hospital with mild disease (i.e. no fever, respiratory distress and sufficient blood oxygen), mean interval between symptom onset and viral clearance was 38.1 days (SD 8.7; range 15 – 62) and was significantly longer amongst patients with digestive symptoms (40.9 days), or both digestive and respiratory symptoms (42.0 days), $p < 0.001$.[507] A meta-analysis conducted to assess viral shedding time (VST) reported the pooled mean VST from 35 included articles was 16.8 days (95% CI 14.8-19.4), with significantly longer VST in patients with symptomatic infection compared to asymptomatic patients (19.7 days, 95% CI 17.2-22.7 vs 10.9 days, 95% CI 8.3-14.3; $p<0.05$). Additionally, longer VST was observed for adults, and those with chronic disease. Viral shedding lasted significantly longer in stool samples than in respiratory samples (30.3 days, 95% CI 23.1-39.2, vs 17.5 days, 95% CI 14.9-20.6; $p<0.05$).[508] A meta-analysis of 1,266 adult respiratory tract samples found severity of disease was associated with increased viral load.[479]

Prolonged viral RNA detection is an issue where discharge/release from isolation is reliant on 2 consecutive negative PCR results. Analysis of a small cohort of cases in Wuhan that returned home after a 14 day isolation period following hospitalisation and were still PCR-positive found no onward transmission to household contacts.[509] None of the household contacts developed any symptoms and both PCR and IgM/IgG antibody testing were negative. Median time of PCR-positivity was 78 days (IQR 67.7-84.5) with the longest duration found to be 120 days. A larger Wuhan cohort (n=2,466) that had a repeat positive PCR test following discharge from hospital had 4,079 close contacts – none of the close contacts had a positive PCR result, suggesting the risk of transmission from prolonged shedders may be small.[510] Discharge was dependent on 2 negative PCR tests taken 24 hrs apart; this implies that either false-negatives were occurring or that shedding fluctuated over time. In a separate study, exhaled breath condensate samples collected ~40 days post-symptom onset from 2 elderly hospitalised patients (medium/severe disease) that met the requirements for discharge (negative PCR throat swab and clinically well) tested positive however these samples were not cultured to test viability.[511] Repeat testing with a larger sample size would provide a more reliable evidence base regarding exhaled breath condensate sampling. Air sampling performed whilst carrying

out tracheostomies on 8 COVID-19 patients that had subsequently tested PCR negative (2 negative tests) identified one positive air sample, collected in the vicinity of a patient that was 17 days post-symptom onset.[512] It is important that COVID status of a patient, even if recently tested negative, is reported to the receiving unit/department prior to transfer/discharge and an assessment of infectious status is carried out on arrival by receiving teams.

Prolonged viral shedding may not correlate with infectiousness; there is limited evidence regarding this as the infectious dose required for transmission has yet to be determined. Wolfel et al assessed 9 cases in Munich, Germany and found that live virus could be isolated from respiratory samples taken within the first 7 days of symptoms but not from day 8 onwards, *even though viral RNA could still be detected in samples*.[163] Live virus isolation may also be dependent on viral load; samples containing under 10^6 copies/mL (or copies per sample) never yielded an isolate.[163] In the absence of histopathology, the same study analysed the presence of viral sgRNA which is only transcribed in infected cells and therefore can indicate the presence of actively-infected cells in samples. Throat swabs taken up to day 5 were positive while no sgRNA was detected thereafter. This suggests that as viral load reduces in the later stages of infection, so too does transmission risk. This was demonstrated in a US cohort of HCWs in which viral load peaked in the first few days after symptom onset then became negatively associated with days since symptom onset, reducing significantly by day 10.[513] Wolfel et al estimate that, for patients beyond day 10 of symptoms and with less than 100,000 viral RNA copies per ml of sputum, early discharge with ensuing home isolation might be appropriate.[163] Analysis of sgRNA in samples from a patient cohort (n=35) with mild infection found it was detectable in 18/22 (81.8%) of specimens collected <8 days after symptom onset but only in 1/11 (9.1%) of those collected >9 days after symptom onset (P=0.0003).[514] The median viral load in culture-positive samples was significantly higher than in culture-negative samples (p=0.00001). Analysis of 754 samples from 425 symptomatic cases in the UK found that levels of viral RNA (determined from the RT-PCR cycle threshold values) in the upper respiratory tract were greatest around symptom onset, steadily decreased during the first 10 days after symptom onset and then plateaued.[515] Detection of culturable virus peaked around the time of symptom onset; median duration of virus shedding as measured by culture was 4 days (IQR 1-8, range -13 to 12). Culture positivity rate was significantly higher during week 1 than week 2 (74% vs 20%, p=0.002). Ten days after symptom onset, the probability of culturing virus declined to 6.0% (95% CI: 0.9–31.2%). A Canadian study found there was no growth on viral culture from samples taken >8 days since symptom onset; the probability of obtaining a positive viral culture peaked on day 3 and decreased from that point.[516] Vero cell infectivity was only observed for samples with a cycle threshold value <24. A further study that

conducted viral culture of 46 cases reported a mean duration from symptom onset to culture positivity of 4.5 days (range 0-18 days); whilst one patient continued to be culture positive to day 18, no others were positive beyond 10 days after symptom onset.[517] Cultures were significantly more likely to be positive from samples collected within the first week after symptom onset when compared to the second week (80% vs 45%, p=0·002), and from samples collected in the second week compared to the third week (45% vs 4%, p<0·001). Ten days was also reported as the maximum number of days post-symptom onset that viral culture could be demonstrated in positive samples from outpatients with mild infection; samples from moderate to severe hospitalized cases could be cultured up to 32 days post-symptom onset.[518] Prolonged viral culture of up to 22 days following the first positive PCR result has been reported elsewhere and was found to be associated with persistence of symptoms.[519] Viral culture has also been demonstrated in children during early acute illness.[520] A French study that assessed viral culture (n=124 samples) in relation to viral load of PCR clinical samples demonstrated a significant correlation between successful isolation of virus in cell culture and Ct values of 13-17.[521] Culture positive rate then decreased progressively according to Ct values to reach 12% at 33 Ct; no culture was obtained from samples with Ct>34. These findings are similar to those reported elsewhere; the median Ct value associated with recoverable virus in a US hospitalised cohort (n=29) was 18.17 which was significantly lower than the median Ct value that did not correlate with infectious virus recovery (27.5, P<0.0001). Samples with a Ct value below 23 yielded 91.5% virus isolates.[519] Taiwanese data also indicates that samples with Ct values of >32 did not yield culturable virus.[522] Similarly, in a hospitalised Singapore cohort (n=100, 20% required supplemental oxygen),[523] and in an Italian hospitalised cohort (n=83, ~15% supplemental oxygen),[524] no virus was able to be isolated when the Ct value was >30, or when patients were >14 days post symptom onset (or 3 days post symptom resolution). In a small hospitalised cohort (n = 174) in Spain, viable SARS-CoV-2 was detected in samples with high viral load (Ct ≤ 25) in cases with both mild or severe symptoms. Moreover, viable virus was detected in a small proportion (5% of mild cases and 15% of severe cases) of respiratory samples with low viral load (Ct ≥ 35).[497] Viable virus was detected in 7% of sputum samples, 40% of saliva samples and 36% of cough samples in a plaque assay study performed in Canada (hospital and community patients).[480] Samples with Ct vales ≤25 were 78% likely to have infectious virus, whereas 92% of samples with Ct values >25 harboured non-viable virus; mean difference in Ct value between plaque-positive (mean = 29.8) and plaque-negative (mean = 19.0) specimens was statistically different (p <0.0001).[480]

It has been proposed that each centre should perform its own correlation study to aid with determination of infectivity cut-off, which may be used to assist decision making regarding

hospital discharge.[521] However, UK guidance (published 28th October 2020) advises that a single Ct value in the absence of clinical context cannot be relied upon for decision making about a person's infectivity.[525] One study, in contrast to the evidence base described, has demonstrated prolonged infectivity as measured by culture on Vero E6 cells of 73 and 102 days (ct values 26.21 and 27.15 respectively); both cases were elderly and had mild symptoms.[526] Further research is required to determine if these cases are outliers. In summary, the evidence base suggests that culture-positive samples tend to have higher viral loads than culture-negative samples, culture positivity peaks close to symptom onset, and culture positivity (and viral load) significantly decreases ~10 days post symptom onset. The impact of these findings on transmission risk is of obvious interest. Analysis of 282 mild transmission clusters in Spain observed an increased secondary attack rate (24% vs 12%) when the baseline viral load of the index case was 1×10^{10} copies per mL or higher (adjusted odds ratio per log10 increase in viral load 1·3, 95% CI: 1·1–1·5).[471] Analysis of 1,064,004 index cases in England from the period September 2020 to February 2021 suggested that viral load in the index case was an important determinant of positivity in contacts, with PCR-positive tests in contacts associated with higher viral loads in the index case.[527] This was independent of the nature of the contact event (household, work place, event, outdoors), however the analysis was largely limited to symptomatic index cases only. Further research is required in the area of viral isolation and cycle threshold analysis to develop a robust evidence base to assist with discharge decision-making.

Data from a number of studies has demonstrated a pattern with viral clearance with regard to clinical sample type; viral presence in respiratory samples appears to peak in the earlier stages of infection then decreases with time whilst the opposite has been observed with stool samples.[146, 147, 157, 159, 170, 491] Analysis of hospitalized cases in China indicated an association between hypertension and delayed viral clearance.[474, 528] Hypertension is the most frequently reported CV comorbidity associated with COVID-19 infection; hypertensive patients also have a higher mortality rate compared to normotensive patients.[116] This has led to the suggestion that treatment with ACE2 inhibitors (antihypertensive medication) in patients with hypertension might facilitate SARS-CoV-2 to enter the targeted cells via ACE2 receptors in the respiratory system, and thus prolong the time of viral clearance.[474] Further research is required to detangle the association between severe disease, comorbidities, and delayed viral clearance.

Reports that suggest possible infectivity in the asymptomatic period are based on limited evidence from largely retrospective observations during contact tracing, and identification of viral RNA in clinical samples post symptom resolution.[10, 146, 167, 355, 356, 464, 529-531]

Concerns over risk of transmission in the incubation period have been raised following identification of possible transmission events in the incubation period from contact tracing studies, and observations of positive clinical samples prior to symptom onset. A report from a long term care facility in which two rounds of 'point prevalence' COVID-19 screening were carried out (1 week apart), found that more than half the residents (27 of 48) who had positive tests were asymptomatic at testing.[532] Further,17 of 24 specimens (71%) from pre-symptomatic persons (those who were asymptomatic at testing but went onto develop disease) had viable virus by culture 1 to 6 days before the development of symptoms. Possible transmission events from these individuals were not reported. Identification of RT-PCR positivity in the incubation period has also been reported in South Korea; 41 out of 213 tested (19.2%) were asymptomatic at testing.[533] Progression to disease was not reported; all individuals were isolated therefore transmission events in this cohort were not assessed. Pre-symptomatic infection with cytopathic effort observed on cell culture was reported from a case in Sweden, which infers infectivity in the pre-symptomatic period.[534] Unfortunately, contact tracing studies frequently lack accompanying clinical data i.e. RT-PCR testing from the incubation period, due to their retrospective nature.

Knowledge is also limited regarding the transmission dynamics of asymptomatic-positive cases. A progressive decline in viral load from day of detection to day of last positivity is a similar pattern to that seen in symptomatic positive cases.[359, 535] Analysis of the initial RNA load and threshold cycle value ('Ct' value, which is inversely proportional to the viral load) from a number of small studies indicates a lower viral load in asymptomatic cases during hospitalisation.[170, 358, 393, 484, 536] In one study, symptomatic cases had an approximately 200-fold higher viral load.[393] However, a larger study found that the initial threshold cycle value of nasopharyngeal RNA in asymptomatic carriers was similar to that in pre-symptomatic and symptomatic patients, but that viral clearance was faster, as the RNA negative-conversion occurred earlier for asymptomatic cases.[364] From this, the authors deduced that the communicable period of asymptomatic cases was shorter than pre-symptomatic patients (9.63 days vs.13.6 days). Significantly faster viral clearance in asymptomatic cases has been demonstrated in a number of small studies.[99, 358] Analysis of 82 Chinese cases found that those with respiratory symptoms (cough) had a statistically significantly longer duration of positive testing by nasopharyngeal swab compared to patients presenting without respiratory symptoms (17 days vs. 13 days, $p = 0.041$).[537]

In general, the evidence regarding the transmission dynamics from asymptomatic cases is weak; further research is required.

Guidance from the ECDC recommends that COVID-19 patients may be discharged from hospital based on: a) clinical resolution of symptoms; b) time elapsed since symptom onset; c) severity of disease; d) immune status; and e) evidence of viral RNA clearance from the upper respiratory tract.[538] Two consecutive negative RT-PCR tests from respiratory specimens at 24 hrs interval are recommended for the discontinuation of isolation for immunocompromised cases and for severely ill patients – especially if being discharged to a long term care facility.[538] The second RT-PCR test is to rule out the possibility of a false negative result. In the first iteration of the ECDC guidance it was recommended that where there is widespread community transmission, clinical criteria should gain priority.[539] This is consistent with Scottish and UK guidance which recommend discharge as soon as the patient is clinical well enough (i.e. symptoms may still be present).[419, 540] Those discharged should self-isolate for 14 days (minimum) from symptom onset (or first positive test if symptoms onset undetermined), with absence of fever for 48 hours without the use of antipyretics.[419] Asymptomatic individuals who test positive for SARS-CoV-2 through routine PCR testing on admission to hospital for non-COVID-19 reasons, can be advised on discharge to self-isolate for 10 days from their positive PCR test, and to isolate for a further 10 days, if the individual goes on to develop COVID-19 symptoms.[540] However, patients being discharged into a care facility (residential or care home) should have 2 negative tests prior to discharge, unless there are overriding clinical reasons where this is not appropriate (patient doesn't consent or it would cause distress).[419] A 14-day isolation period is required for asymptomatic patients discharged to a care facility.[419]

Conclusion:

- Transmission is most likely to occur whilst an individual is symptomatic.
- In mild cases of infection, where hospitalisation is not required, the risk of transmission is thought to significantly reduce after 7 days.
- Individuals with symptoms consistent with COVID-19 should self-isolate for 10 days from symptom onset.
- In severe cases the risk of transmission may extend beyond 7 days therefore Transmission Based Precautions (TBPs) should remain in place for the duration of hospital admission or home isolation until cessation of symptoms.
- In hospital settings clinicians should consider extending isolation for some cases e.g. elderly, immunosuppressed, if they remain symptomatic after 14 days until test results are available.

- Patients discharged from hospital should self-isolate for 14 days from symptom onset (or first positive test if symptom onset undetermined) with absence of fever (without use of antipyretics) for 48 hours.

5. Personal protective equipment

5.1 Evidence for mask type

There are two main categories of masks worn by HCWs; 1) surgical face masks, and 2) respirators. Surgical face masks do not provide protection against airborne particles and are not classified as respiratory protective devices[541] therefore respirators are typically reserved for protection against airborne infectious agents. The historical dichotomy of 'droplet' versus 'airborne' transmission mode resulted in a mutually exclusive relationship between transmission mode and mask type (surgical face mask for droplet transmission, and respirators for airborne transmission).

With regards to surgical face masks, it is vital that a distinction is made between the evidence pertaining to fluid-resistant surgical face masks (FRSM) (Type IIR) and standard (non-fluid-resistant) surgical face masks (Types I & II). Surgical masks are tested against the safety standard BS EN 14683:2019; this series of tests measures the performance of a surgical mask in bacterial filtration efficiency (BFE), breathing resistance and splash resistance. Type II and Type IIR surgical masks are both tested against this standard with them needing to meet a minimum BFE of 98%; however only Type IIR masks must pass the splash resistance test with a resistance of at least 16.0kPa. The terms 'fluid resistant' and 'fluid repellent' are often used interchangeably to denote a Type IIR surgical mask, however, terminology may vary internationally and a 'fluid repellent' mask may occasionally describe a mask that does not meet the BS EN 14683:2019 splash resistance standard and which is not suitable for protection against splash or spray i.e. a Type II surgical mask. In the UK, when recommended for infection prevention and control purposes a 'surgical mask' will be a fluid-resistant (Type IIR) surgical mask.

5.1.1 Face masks for source control

Standard surgical face masks (i.e. Type II) can be worn by an infectious individual as source control to prevent transmission.[542-544] To demonstrate this, a study by *Leung et al* tested the efficacy of surgical masks at reducing the detection of seasonal (non-COVID-19) coronavirus in exhaled breath from infected patients.[545] Coronavirus could be detected in ~40% of samples collected from non-mask wearers (n=10) but was not detected in exhaled air from patients that wore surgical masks (n=11). The masks used were Type II, i.e. they were not fluid-resistant. This study was limited by the small sample size – due in part to the fact that a large proportion of infected participants had undetectable viral shedding in exhaled breath. Studies assessing Type II surgical masks have also reported reduced detection of seasonal influenza in exhaled breath in mask wearers.[545, 546] An environmental sampling study of multiple sites (prior to environmental cleaning) surrounding 3 hospitalised COVID-19 patients yielded negative results; two of these patients wore surgical masks continually and the critical bed-bound ICU patient had a closed loop circuit ventilator.[547] All patients tested positive by throat swab on the day of sampling and the masks and the closed suction tube tested positive.

In regards to source control, an experimental study using 12 healthy volunteers found that air escape from the sides/top of a 3-layer pleated surgical mask led to a reduction in efficiency from >90% (for air that passes through the mask) to ~70% while talking and a reduction from 94% to 90% for coughing.[548] This demonstrated that whilst air escape does limit the overall efficiency of surgical masks at reducing expiratory particle emissions, masks do provide substantial reduction. Using healthy volunteers in an experimental set up, a fluid resistant surgical mask was found to significantly reduce aerosol emissions from both speaking (0.113 vs 0.038, $p = 0.002$), and coughing (1.40 vs 0.075, $p < 0.001$).[70] An experimental study using simulated SARS-CoV-2 virus expulsions and mannequin heads demonstrated a synergistic protective effect when both the spreader and receiver wore a mask (cotton or surgical), suggesting that universal face covering/mask wearing is likely to have a protective effect overall.[549]

Concern has been raised regarding the suitability of respirators for providing source control, specifically where respirators are fitted with exhalation valves that offer no filtration of exhaled air. It is stated in the NIPCM that respirators must never be worn by an infectious patient due to the nature of the respirator filtrating incoming air rather than expelled air.[550] The ECDC, CDC, and WHO advise against the use of respirators with exhalation valves for source control of COVID-19.[551-553] A recent **ARHAI Scotland rapid review** that assessed respirators demonstrated consistency in the evidence that valved respirators should not be used for source control. It must therefore be acknowledged that there is a risk that staff later identified as

infectious whilst wearing a valved respirator may have presented an exposure risk to patients and staff if within 2 metres.

5.1.2 Face masks for protection

Whereas standard Type II surgical face masks can be worn by an infectious individual to prevent transmission, it is the fluid-resistant nature of FRSMs that provides additional protection to the wearer (e.g. HCW) against droplet-transmitted infectious agents. Guidance consistently recommends that HCWs should wear a Type IIR FRSM as PPE when caring for a patient known, or suspected, to be infected with an infectious agent spread by the droplet route.[66, 542, 544, 554-558] In UK health and care settings, surgical masks must be fluid-resistant, 'CE' marked and compliant with Medical Device Directive (MDD/93/42/EEC) and the Personal Protective Equipment Regulations 2002.[559-564]

When assessing the infection risk related to surgical masks and respirators, there is no clear evidence that respirators offer any additional protection against coronaviruses. A major limitation is that the majority of evidence is observational in nature and thus is clouded by bundled infection control approaches, poor descriptions of mask types (with a focus on comparison to FFP2 rather than FFP3 respirators) and an unclear distinction between AGP and non-AGP care. Assessment of PPE use against similar coronaviruses i.e. severe acute respiratory virus (SARS), provided weak evidence that droplet precautions (i.e. surgical face masks) are adequate. A systematic review and meta-analysis combining 6 case-control and 3 cohort studies, found that use of respirators/surgical masks provided significant protection against SARS-CoV among exposed HCWs (OR=0.22; 95% CI: 0.12-0.40). Wearing surgical masks (OR=0.13; 95% CI: 0.03-0.62) or N95 respirators (OR=0.12; 95% CI: 0.06-0.26) (versus no RPE) both reduced the risk of SARS-CoV by approximately 80%. No protective effect was reported for disposable cotton or paper masks. The existing evidence base in the review was sparse and the indications (and compliance) for mask/respirator use varied between the included studies.[565] The type of surgical mask was not reported in all studies. A case control study that compared PPE use in 241 non-infected HCWs and 13 infected HCWs with documented exposure to 11 index patients with SARS-CoV found that none of the infected staff wore surgical masks or respirators (2 wore paper masks). [566] However, RT-PCR analysis was not used to confirm infection in this study (confirmation of HCWs relied on serological analysis), and recall bias for PPE use may have affected results. Inadequate reporting of RPE/mask indications and compliance was a major limitation in a systematic review and meta-analysis conducted by *Bartoszko et al*, which included 4 RCTs and reported that, compared to N95

respirators, the use of medical masks was not associated with an increase in laboratory-confirmed viral respiratory infection or respiratory illness.[567] There was significant variation in surgical mask type between the included studies (Type IIR FRSMs were not used in every study). A rapid review conducted specifically to assess the RPE requirements for COVID-19 in primary care determined that the evidence base was weak as the included studies were focussed on influenza transmission, not COVID-19; these studies provided weak support for the use of standard surgical masks in non-AGP settings.[568] A recent update to a Cochrane systematic review that assessed full body PPE for the prevention of exposure to highly infectious diseases (including COVID-19) found that covering more parts of the body leads to better protection but usually comes at the cost of more difficult donning or doffing and less user comfort, and may therefore even lead to more contamination.[569] Certainty of the evidence was judged as low due to the fact that almost all findings were based on one or at most two small simulation studies.

An observational study that collected self-report data regarding preferred mask use (surgical or FFP2) of healthcare workers in Switzerland found that FFP2 preference whilst caring for COVID-19 patients was non-significantly associated with a decreased risk for SARS-CoV-2 positivity (adjusted hazard ratio [aHR] 0·8, 95% CI 0·6-1·0, p=0·052).[570] The factor most strongly associated with a positive SARS-CoV-2 test was exposure to a positive household contact (adjusted HR [aHR] 10·1, 95% CI 7·5-13·5, p<0·001). This study was not able to definitively show that HCWs acquired infection as a result of their work, further, participation in the study was non-mandatory and compliance with stated mask preference was not assessed. In a US HCW cohort (n=345), the most common reason for a significant exposure to a COVID-19 patient was use of a surgical mask instead of a respirator during an AGP (206/345, 55.9%), however this was not associated with testing positive (RR 0.99, 95% CI 0.96-1, P=1).[571] When assessing such studies it is a heuristic bias to assume that PPE provision (or lack of) is the sole reason for transmission; multiple factors determine the risk of transmission from one individual to another (including for example infectiousness of the patient, viral load, infectious dose, contact time). An example of this is a recently published (June 2021) pre-print study where HCW infection rates were considered after the introduction of unit-wide FFP3 respirators instead of surgical face masks (type IIR) for “red” wards in an English hospital; twice-weekly testing and vaccination were introduced at the same time as the FFP3 respirators, which is likely to have confounded the outcomes.[572] The small sample size and poor methodology of the study are further limitations.

The Australian National COVID-19 Clinical Evidence Taskforce recently published a living systematic literature review on the topic of RPE/surgical masks but was unable to produce

evidence-based graded recommendations due to the limited evidence base.[573] Only 1 randomised trial was included to inform the Australian RPE recommendations and this study only assessed coronaviruses OC43, 229E, NL63 and HKU1. In the surgical masks group the infection rate was 493 per 1000, compared to 571 per 1000 in the P2/N95 group, with an odds ratio of 0.73 (95% CI 0.30-1.77). The certainty of the evidence was rated as low due to serious indirectness and serious imprecision. A total of 17 observational studies were included that reported on both SARS-CoV-1 (n=5) and SARS-CoV-2 (n=12). The rate of infection in the surgical mask group was 50 per 1000, and in the P2/N95 group was 39 per 1000, with an odds ratio of 1.34 (CI 96% 1.06-1.70). The certainty of the evidence was rated very low due to serious risk of bias, serious indirectness and serious imprecision. The inclusion of observational studies in the Australian guideline meta-analysis, plus the inclusion of studies reporting on SARS-CoV-1 can be criticised however the evidence has been appropriately rated as low/very low quality by the critical appraisal tools and this is reported in the evidence summary by the authors. As a result of the low quality evidence base, consensus recommendations, rather than evidence-based recommendations, were developed. None of the studies identified in the Australian review involved use of FFP3 respirators (all were N95/FFP2/P2), and this is a limitation relevant for Scotland/UK where use of FFP3 respirators are mandatory over other respirator types as per the Health & Safety Executive (HSE). Whilst an FFP3 respirator is the recommended RPE for use in the UK, it may not be reasonably practicable to use these if global supplies of FFP3 respirators are low during a pandemic. In this scenario, the WHO advise that an FFP2 could be used as an alternative. In March 2021, the UK Health and Safety Executive concluded in a rapid review that N95 respirators (used out with the UK) were comparable to FFP2 respirators and that both would provide comparable protection against coronavirus as long as the wearer was face-fit tested.[574]

Australian consensus recommendations for face masks state that for HCWs providing direct patient care or working within the patient/client/resident zone for individuals with suspected or confirmed COVID-19, the choice between P2/N95 respirator or surgical mask should be based on an assessment of risk of transmission.[573] The risk assessment should include consideration of: the individual patient/client/resident's pre-existing likelihood of COVID-19; current prevalence and transmission of COVID-19 in the population; setting-specific factors such as the likelihood of increased generation and dispersion of airborne particles and enclosed areas with low levels of ventilation; and closeness and duration of contact.[573] It is important to note that the Australian consensus recommendations were made in a time of low community prevalence when asymptomatic individuals were not classified as suspected cases.

Further advocating the use of a risk assessment with regard to RPE and transmission risk, SAGE in April 2021 advised that if an unacceptable risk of transmission remains after rigorous application of the hierarchy of controls it may be necessary to consider the extended use of RPE for patient care in specific situations, taking into consideration the likelihood, duration and proximity of exposure to a COVID-19 case and what other measures have been applied in the setting.[25] This is in acknowledgement of the risk of aerosol transmission out with AGPs. In response, Scottish guidance was updated in May 2021 to include further detail on risk assessments applied using the hierarchy of controls for inpatient wards selected for planned placement of the high risk pathway, with extended use of RPE a possible outcome of such a risk assessment.[419] A risk assessment algorithm was added in July 2021.

The World Health Organization, Canadian Government guidance, and Australian Government guidance recommends surgical face masks for routine care (non-AGP) of suspected/confirmed COVID-19 patients.[575-578] The US Centers for Disease Control and Prevention (CDC) recommend that HCWs can wear a well-fitting facemask for protection during non-AGP patient care encounters with patients not suspected of having COVID-19 (respirators are optional).[579] This would equate to care for patients on the low risk (green) pathway in the UK. In the 6th update of ECDC IPC guidance, respirators rather than surgical masks are recommended when caring for suspected/confirmed patients.[18] The ECDC make reference to the weak evidence base underpinning their recommendation, stating that "*with the exception of AGPs, it is unclear whether respirators provide better protection than medical masks against other coronaviruses and respiratory viruses such as influenza*".[18]

The UK Scientific Advisory Group for Emergencies (SAGE) acknowledged that the impact of greater use of FFP3 masks on the overall level of transmission in HCWs is unknown, but that this should not be taken to show an absence of effect, stating that policy-makers may have to make decisions based on a range of additional factors.[406]

Guidance issued by the Scottish Government on 23rd June 2020 advised that all staff in hospitals and care homes in Scotland are required to wear a 'medical' face mask at all times throughout their shift, from 29th June 2020 onwards.[580] Face mask/covering requirements were extended to include primary care (GP practices, dentists, opticians and pharmacies) and wider community care (including adult social or community care and adult residential settings, care home settings and domiciliary care) on 18th September 2020. Patients and visitors to hospitals and care homes must wear a face covering. This guidance was updated on 5th July 2021 to state that staff in clinical and non-clinical areas of hospitals are specifically required to wear a type IIR fluid resistant surgical face mask (FRSM).[581] Additionally, FRSMs must also be made

available to and worn by all hospital inpatients (unless exempt) across all pathways, where it can be tolerated and does not compromise clinical care (e.g. when receiving oxygen therapy or when in labour). Visitors to care homes must also wear FRSMs. These measures are in recognition of the risk of pre-symptomatic and asymptomatic transmission, and the difficulties in maintaining physical distancing in the workplace. These recommendations are in-line with guidance produced by the World Health Organization, which states that in areas of known/suspected community or cluster transmission, universal masking should be implemented for all persons (staff, patients, visitors, service providers, others) within the health facility.[20] This was based on expert opinion. It should be noted that the fluid resistant component of masks is not required for source control however, guidance in Scotland advises use of fluid resistant surgical masks (Type IIR) at all times to avoid confusion and error in mask selection moving between direct patient care activities and general circulation within healthcare facilities.

The Scottish COVID-19 addendum for acute care settings published within the NIPCM on October 27th 2020 states that HCWs should wear a type IIR fluid resistant surgical mask for all direct contact with patients, and when carrying out AGPs in the green pathway.[419]

The UK Health and Safety Executive (HSE) position regarding RPE has remained unchanged; currently the use of respirators, such as FFP2 or FFP3, are only for the highest risk aerosol generating procedures which are undertaken in medical settings and during dental procedures (*correspondence provided by the UK IPC Cell*). The Scottish COVID-19 Addendum advises that respirators are worn by HCWs when carrying out AGPs in medium and high risk pathways. At all other times, HCWs are expected to be wearing Type IIR fluid-resistant surgical face masks. However, in recognition of the anxiety felt by many HCWs with regards to PPE provision, Scottish guidance recommends that where staff have concerns about potential exposure to themselves, they may choose to wear an FFP3 respirator rather than an FRSM when performing an AGP on a low-risk pathway patient; this is a personal PPE risk assessment.

It is important to note that not all FFP3 respirators are fluid-resistant; valved respirators can be shrouded or unshrouded. Respirators with unshrouded valves are not considered to be fluid-resistant and therefore should be worn with a full face shield if blood or body fluid splashing is anticipated. This must be taken into consideration where FFP3 respirators are being used for protection against COVID-19 transmission. UK and Scottish COVID-19 guidance further clarifies that valved respirators should not be worn by HCWs when sterility over the surgical field is required as exhaled breath is unfiltered e.g. in theatres/surgical settings or when undertaking a sterile procedure.[419, 582] This is a consideration that extends beyond COVID-19 and takes account of potential surgical site infection risk.

Note: the evidence base regarding respirator use is further detailed in the **ARHAI Scotland respirators rapid review.**

Conclusion:

- HCWs should wear a type IIR fluid-resistant surgical face mask during any activities/procedures where there is a risk of blood, body fluids, secretions or excretions splashing or spraying onto their nose or mouth.
- HCWs across all pathways should wear a type IIR fluid-resistant surgical face mask throughout their shift.
- Non-medical staff and HCWs off duty/out-with clinical areas should wear a type IIR FRSM at all times whilst at work except in some circumstances, e.g. when working alone; or in a closed office where other transmission measures are in place (i.e. physical distancing; ventilation; access to hand washing facilities, and regular cleaning).
- Inpatients across all pathways should wear a type IIR fluid-resistant surgical mask at all times if they can be tolerated and care is not compromised.
- Airborne precautions (FFP3 respirators) are required when performing AGPs on patients in the medium risk (amber) and high risk (red) pathways.
- HCWs may choose to wear an FFP3 respirator rather than an FRSM when performing an AGP on a low-risk pathway patient; this is a personal PPE risk assessment.
- The unit-wide use of FFP3 respirators should be considered in clinical areas used for the high risk pathway where there remains an unacceptable risk of transmission despite application of mitigation measures following a risk assessment as per the NIPCM COVID-19 Acute care addendum.
- A non-valved (rather than a valved) respirator should be worn when sterility directly over a surgical field/sterile site is required.
- The use of FFP2 respirators should be considered where there are shortages of FFP3 respirators.
- All patients and visitors entering a healthcare setting should wear a face covering.
- All visitors entering a care home should wear a type IIR fluid-resistant surgical mask.

5.2 Face visors

The Scottish COVID-19 addendum for acute settings (published 27th October 2020) recommends that eye/face protection should be worn at all times during direct contact in high-risk (red) pathways and this is always in combination with a face mask or respirator.[419] For low-risk (green) and medium-risk (amber) pathways, eye/face protection is only required if splashing or spraying with blood and/or body fluids is anticipated and again, this is always in combination with a face mask. Whilst the NIPCM Chapter 1 currently states that for SICPs a face visor can be used without a face covering to provide eye/face protection against splash and spray, at no point should a face visor be worn in place of a face mask when providing care on any of the three COVID-19 pathways. There is some evidence from experimental studies to support that face visors alone are less effective than other forms of face protection at preventing influx of exhaled droplets/aerosols; these are covered in more detail in the **eye protection rapid review**. This is also the case for source control; an experimental study found that a face shield blocked only 2% of experimentally exhaled cough aerosols compared to 59% blocked by a fluid-resistant face mask and 51% blocked by a 3-ply cotton face covering.[583] The World Health Organization advises that face shields are considered to provide a level of eye protection only and should not be considered as equivalent to masks with respect to respiratory droplet protection and/or source control.[20] The Health and Safety Executive (HSE) advises that in the event of severe shortages of medical masks, face shields may be considered as an alternative, but that they cannot be used as a substitute for respiratory protection.[584] Face visors may act as a barrier to face touching, however adherence to appropriate hand hygiene at all times as well as when donning and doffing PPE is essential to reduce the risk of indirect contact transmission.

Conclusion:

- Eye/face protection should be worn if splashing or spraying with blood and/or body fluids is anticipated.
- Eye/face protection should be worn when within 2 metres of patients in high-risk (red) pathways.
- A face visor should not be worn in place of a surgical face mask or respirator in the context of COVID-19.

5.3 UK PPE guidance

For general patient care (i.e. non-AGP situations), the first edition of the UK IPC pandemic COVID-19 guidance initially recommended type IIR FRSMs, disposable aprons and disposable gloves.[14] The decision to wear eye protection was based on risk assessment (but considered essential when carrying out AGPs). Fluid-resistant long sleeve gowns were recommended for management of confirmed cases and when carrying out AGPs.[14] FFP3 respirators were recommended when carrying out AGPs and when in high risk areas where AGPs are being conducted. The FFP3 recommendation was based on expert opinion from NERVTAG which recommended that airborne precautions should be implemented at all times in clinical areas considered AGP 'hot spots' e.g. Intensive Care Units (ICU), Intensive Therapy Units (ITU) or High Dependency Units (HDU) that are managing COVID-19 patients (unless patients are isolated in a negative pressure isolation room/or single room, where only staff entering the room need wear a FFP3 respirator).

The UK IPC pandemic COVID-19 guidance was updated on 2nd April 2020 with a move to PPE based on risk of exposure to possible (not suspected/confirmed) cases, with recommended ensembles for specific care areas/clinical situations.[585] The guidance stated that '*incidence of COVID-19 varies across the UK and risk is not uniform and so elements of the updated guidance are intended for interpretation and application dependent on local assessment of risk*'. While this was not in line with the evidence base at that time for COVID-19 as presented in this rapid review, it was based on the potential challenges in establishing whether patients and individuals meet the case definition for COVID-19 prior to a face-to-face assessment or care episode. There was also a move towards sessional use of PPE considering the recognised global shortage of PPE stockpiles at the time and perhaps in recognition of the fact that the change in UK PPE recommendations were likely to result in greater use of PPE by a wider staff group which would deplete existing UK stocks.

UK PPE guidance published by PHE was updated on 20th August 2020 with the publication of IPC guidance for remobilisation of service in health and care settings.[586] A major change was the introduction of 3 patient pathways for COVID-19 which set out the PPE requirements for each area. The guidance was updated and renamed to '*Guidance for maintaining services within health and care settings*' on 21st January 2021[587] with the latest version 1.2 published on 1st June 2021.[582] Whilst sessional use of single use PPE/RPE items continued to be minimised in the recommendations, the guidance states that sessional or extended use of facemasks (all pathways) or FFP3 respirators (together with eye/face protection) can be applied in the medium

and high risk pathways where airborne precautions are indicated e.g. AGPs undertaken for COVID-19 cohorted patients/individuals.[582]

Scottish COVID-19 guidance (in the form of an addendum) was published in the NIPCM on 27th October 2020 and also includes the implementation of 3 patient pathways. There is a return to SICPs-based PPE, with PPE usage dictated by anticipated blood and/or body fluid exposure, and respirators only required for AGPs on patients in the amber and red pathways. As per the PHE UK guidance, there is no longer a requirement in Scottish settings for sessional PPE use, apart from FRSMs which can be worn sessionally. The addendum advises that consideration may need to be given to unit-wide application of airborne precautions where the number of cases of high and medium-risk pathway patients requiring AGPs increases and all such patients cannot be managed in a single side room. In recognition of the anxiety felt by many HCWs with regards to PPE provision, Scottish guidance recommends that when prevalence is high, and where staff have concerns about potential exposure to themselves, they may choose to wear an FFP3 respirator rather than an FRSM when performing an AGP on a low-risk pathway patient; this is a personal PPE risk assessment. In June 2021, this recommendation was amended with the removal of the requirement for prevalence to be high when making a personal PPE risk assessment for FFP3 use for AGPs on low risk pathways. In response, Scottish guidance was updated in May 2021 to include further detail on risk assessments applied using the hierarchy of controls for inpatient wards selected for planned placement of the high risk pathway, with extended use of RPE a possible outcome of such a risk assessment.[419] A risk assessment algorithm was added in July 2021.

Reuse of PPE (FFP3/FF2/N95 respirators, fluid-resistant gowns or coveralls, goggles and face visors) as advised for periods of PPE shortages in a previous version of the IPC guidance in April 17th 2020, is no longer recommended in Scottish settings.[1]

The Scottish and UK PPE guidelines remain in line with those issued by the World Health Organization.

The safety and efficacy of extended use or re-use of PPE has not been extensively studied. An evidence summary by ECRI (Emergency Care Research Institute), a US company that

[1] As of October 2020, evidence regarding methods for the decontamination of respirators is being collated but no longer reviewed for this rapid review. A targeted rapid review on the subject will be undertaken should the need arise.

evaluates medical devices, evaluated 21 laboratory studies and concluded that extended use (i.e. sessional use) of N95 respirators was preferable to reuse.[588] Mechanical failure (e.g. broken straps and poor sealing between the mask and the user's face) following only a few reuses was common across a number of FDA-cleared N95 respirators. The reported pathogen transfer risk from contact during donning and doffing during reuse was considered to be higher than the risk from sessional wear. Use of surgical masks or similar disposable covers over N95s during sessional wear were unlikely to result in significant adverse effects. Reuse would require disinfection however loss of filter performance was reported with some common disinfection methods. The methods for disinfection included humid heat, chemical disinfection, and ultraviolet germicidal irradiation (UVGI). The ECRI report summarises the findings from a number of decontamination studies conducted; steam sterilisation required 10 minutes at a minimum of 121°C to be effective however it may damage polymer fibres in the filter and compromise performance; chemical disinfection was limited by the risk of toxicity and chemical incompatibility with filter materials; UVGI penetration may be incomplete in multi-layered N95 filters, which has been evidenced experimentally.[589] UVGI is capable of inactivating coronaviruses including MERS-CoV and SARS-CoV however these tests were not conducted on any type of PPE.[590] UV radiation degrades polymers which presents the possibility that UVGI exposure may reduce the efficacy of respirators.[591] A previous study demonstrated degradation of 4 different types of N95 respirators at doses of 120-950 J/cm^2.[592] Attempts at using steam sterilisation of FFP respirators has shown promise however rigorous testing in line with EN standards for respirator efficacy is required.[593] In a separate study, heat treatment at 70°C at either 0% or 50% humidity did not appear to damage N95 masks nor compromise fit performance, however this study only measured the efficacy of this method at removing SARS-CoV-2 from respirators by using respirator material that had been cut into 1cm^2 pieces.[594] None of the eight different decontamination methods that were tested on different N95 respirator models were suitable, failing in terms of ability to penetrate the filters and/or as a result of damage to the respirators.[595] The methods included UVGI, ethylene oxide, hydrogen peroxide gas plasma, hydrogen peroxide vapour, microwave-oven-generated steam, bleach, liquid hydrogen peroxide, and moist heat incubation (pasteurization). Disinfection using aerosolised peracetic acid and hydrogen peroxide vapour was found to be effective at reducing contamination of a surrogate coronavirus bacteriophage on N95 respirators.[596] Use of vaporised hydrogen peroxide was also found to be suitable for N95 respirator decontamination using an experimental inoculum of SARS-CoV-2 with a cycle threshold value of 20–22.[597] Notably, the safety of these chemicals for this purpose has not been tested and decontamination should be tested on naturally contaminated PPE, as experimental

contamination may not be representative of the levels of contamination experienced in real-life clinical scenarios.

UK IPC pandemic COVID-19 guidance has never recommended decontamination of respirators.[585] Respirators should be discarded if they become moist, visibly soiled, damaged, or become hard to breathe through. The ECDC recommends that, where reuse of respirators is considered as a last resort option to economise on use of PPE, the risk of the surface of the respirator becoming contaminated by respiratory droplets is considered to be lower when it is covered with a visor.[598] However this ensemble is dependent on a plentiful supply of visors.

As highlighted in the ECRI report, the reported pathogen transfer risk from contact during donning and doffing during reuse was considered to be higher than the risk from sessional wear.[588] Unfortunately there is no evidence available to assess the impact on filtration efficacy or the risk of transmission associated with reuse of RPE in clinical settings. A study that assessed efficacy of type IIR FRSMs and N95 respirators that were worn sessionally and reused did not include a reliable control group for comparison which prevented assessment of the efficacy of continuous wear/reuse.[599] RPE was reported to be stored between shifts in a paper bag in lockers; the extent of reuse was not reported. Compared with continuous use of FRSMs, respirators were associated with more problems for the wearer including significantly greater discomfort, trouble communicating with the patient, headaches, difficulty breathing, and pressure on the nose.[599] The WHO '*Rational use of PPE for COVID-19*' mentions that respirators can and have previously been used for extended periods of time to treat multiple patients with the same diagnosis.[600] Whilst WHO state that there is evidence to support respirators maintaining their protection over longer periods of time, it may not be comfortable to use one respirator for longer than 4 hours and this should be avoided[600] as reuse may increase the potential for contamination and contact transmission of infectious agents (not just SARS-CoV-2). This risk must be balanced against the need to provide respiratory protection for HCWs providing care and to those performing AGPs. To reduce the risk of transmission associated with PPE reuse it is essential that HCWs demonstrate stringent compliance with all other infection control precautions, hand hygiene, and environmental decontamination. Irrespective of the measure implemented, HCWs must have IPC education and training on the correct use of PPE and other IPC precautions, including demonstration of competency in appropriate procedures for donning and doffing PPE and hand hygiene. These issues are for consideration by the Health and Safety Executive (HSE). The HSE approved the sessional use and reuse of PPE in the UK for COVID-19 and expects NHS Boards to have an agreed action plan that includes consideration of all measures to manage usage effectively.

Conclusion:

- PPE should be single-use unless otherwise stated by the manufacturer.
- Continuous use of Type IIR surgical face masks in clinical and non-clinical areas is required in line with physical distancing measures.
- Consideration should be given to the unit wide application of airborne precautions where the number of cases of COVID-19 in amber and red pathways requiring AGPs increases and patients/individuals cannot be managed in single or isolation rooms.
- The unit-wide use of FFP3 respirators should be considered in clinical areas used for the high risk pathway where there remains an unacceptable risk of transmission despite application of mitigation measures following a risk assessment as per the NIPCM COVID-19 Acute care addendum.
- In periods of PPE shortages, sessional use of respirators is preferred over reuse.
- In periods of PPE shortages, the decision to reuse PPE (respirators, fluid-resistant gowns or coveralls, goggles and face visors) should be based on a risk assessment considering the care activities, patient population, and the state of the PPE in question.

6. Hand hygiene

Most articles identified recommend that hand hygiene should be performed, however many do not specify the product(s) to be used in preventing the transmission of SARS-CoV-2. A number of guidance documents provide specific recommendations which differ only slightly.[8, 12, 16] WHO and Public Health England support the use of soap and water, and alcohol-based hand rub (ABHR) when soap and water is not available and when hands are not visibly soiled.[12, 16] Experimental evidence has shown that commercially-available ABHRS and WHO ABHR formulations are effective at inactivating SARS-CoV-2 within a contact time of 30 seconds.[601, 602] Commercially-available ABHRs have also shown efficacy against other coronaviruses included SARS-CoV and MERS-CoV.[601, 603]

Conclusion:

- Hand hygiene should be performed with soap and water or, when hands are not visibly soiled, with ABHR.

7. Survival in the environment

A number of environmental sampling studies of rooms/areas occupied by COVID-19 patients and surrounding areas sampled various locations prior to environmental cleaning; viral RNA was found on multiple surfaces including the bed, bed sheets, bed rail, locker, chair, computer table, keyboard, light switches, sink, taps, floor and staff shoes, window ledge, PPE storage area, hand sanitiser dispensers, air outlet fans, elevator buttons, as well as the toilet bowl surface and handle, door handle, and medical equipment (ventilators, monitors, blood pressure cuffs, thermometers, drainage bags, high flow oxygen generator, endotracheal tube, infusion pumps , endoscope).[27-30, 32, 37, 38, 40, 42, 47, 50-52, 55, 62, 63, 511, 604-616] Personal items such as mobile phones, TV remotes, towels and toothbrushes were also contaminated.[28, 50, 62, 63, 605] Overall, positive rates were significantly higher in medical areas compared to office areas and buffer rooms for donning PPE; contamination in these areas was found on telephones, desktops, keyboards, computer mice and water machine buttons.[37, 610] Sampling carried out prior to environmental cleaning across patient care areas and non-patient care areas of an emergency department revealed positive samples in patient care areas only (from stretchers, pulse oximeters, blood pressure cuffs, plastic screens between patients, and the floor).[617] A study that sampled multiple surfaces within an emergency triage unit and a sub-intensive care ward identified positive samples on 2 CPAP helmets only.[618] It is possible that environmental cleaning, carried out 4 hours prior, may have impacted results. Environmental sampling studies are often limited as they omit information regarding frequency of environmental cleaning, or conduct sampling immediately following cleaning.[619-621] Viable virus has been detected in three studies from samples collected from the surfaces of fixtures, fittings and medical equipment in COVID-19 patient rooms[28, 54, 480] but most studies have failed to demonstrate viability.[52, 62, 610, 618, 621] The potential effect of disease progression and viral shedding on environmental contamination has not been investigated extensively, however one study has demonstrated a significant correlation between viral load ranges in clinical samples and positivity rate of environmental samples ($p < 0.001$).[622] When the viral load of clinical samples was higher than or equal to 3 log copies/ml, environmental contamination with SARS-CoV-2 could be detected. However, the sample size in this study was small and further research is required to confirm these findings. Environmental contamination was detected in two hotel rooms occupied by quarantined cases that were pre-symptomatic during their stay, which highlights the risk of environmental contamination from shedding in the pre-symptomatic phase.[623] Viral RNA contamination of high touch surfaces in public places (shops, banks, fuel station) has also been demonstrated but viability was not tested.[624] In general, sampling studies highlight the potential

for environmental contamination, particularly of frequently-touched areas, but the risk of acquiring infection from contaminated environmental sites remains unknown. Very few studies have tested viability of PCR-positive samples obtained from environmental swabbing. Sampling of surfaces considered to be low touch (tops of door frames, tops of shelving units) in a number of long term care facilities in Canada generated positive PCR samples but viability could not be demonstrated in culture; care activities in these settings were not provided in detail.[35] An in-vivo study tested the viability of SARS-CoV-2 under a number of experimental conditions and found that cells remained viable for 3-5 days at room temperature.[625] In light of limited data for SARS-CoV-2 regarding survival time in the environment, evidence was assessed from studies conducted with human coronaviruses including MERS-CoV and SARS-CoV, and human coronavirus 229E. From largely experimental studies, human coronaviruses are capable of surviving on inanimate objects and can remain viable for up to 5 days at temperatures of 22-25°C and relative humidity of 40-50% (which is typical of air conditioned indoor environments).[11, 141, 626-629] Experimental evidence indicates that SARS-CoV-2 survival in the environment is negatively impacted by increasing temperature.[630-632] Survival is also dependent on the surface type.[626, 632-634] Experimental studies using SARS-CoV-2 strains have reported viability on plastics for up to 120 hours, for 72 hours on stainless steel, 120 hours on glass,[635] 24 hours on acrylic,[633] and up to 8 hours on carpet, copper and upholstery.[633, 636, 637] Viability was quantified by end-point titration on Vero E6 cells. An experimental study conducted with human coronavirus 229E found that the virus persisted on Teflon, PVC, ceramic tiles, glass, and stainless steel for at least 5 days (and 3 days for silicon rubber) at 21°C and a relative humidity of 30-40%.[638] Another experimental study performed using 3 variants of SARS-CoV-2 (B.1.1.7, B.1.351 and their common predecessor, EPI_ISL_407073) demonstrated that the virus remained viable for up to 7 days at 19°C and 57% relative humidity following inoculation on stainless steel coupons, with no significant difference in viability once the inoculums had dried ($p = 0.12$). Significantly higher units of the B.1.1.7 and B.1.351 variants were recovered compared to their common predecessor during the drying process ($p = 0.01$), however, further research in this area is necessary to determine the implications of these findings.[639] Infectivity of the persistent viral cells was demonstrated experimentally using a plaque assay in both of these experimental studies, however the infectivity of surface-contaminating SARS-CoV-2 in real-life conditions remains unknown. Experimental testing in the dark (zero UV) found that SARS-CoV-2 could survive for prolonged periods on multiple surface types however the negation of UV is not representative of real-life scenarios and the results of such experiments must be interpreted with caution.[640] Another experimental study detected viable SARS-CoV-2 virus for up to 7 days on hydrophobic surfaces (i.e. stainless steel, Tyvek, disposable gowns, bank notes and surgical masks) and 3 days on hydrophilic surfaces (i.e. cotton and polyester

shirts) at 21°C and average relative humidity of 45%.[634] One study that examined the stability of human coronaviruses on textiles found HCoV-OC43 to remain infectious on polyester for ≥72 hours, on cotton for ≥24 hours, and on polycotton for ≥6hours. Only Polyester was able to demonstrate HCoV-OC43 transfer onto PVC up to 72 h post inoculation, whereas no transfer was detected from cotton or polycotton immediately after inoculation[641]. Survival of human coronaviruses and surrogates in water is influenced by temperature (viral inactivation increases with increasing temperatures) and organic or microbial pollution.[642] A 99.9% viral titre reduction was observed after 2-3 days in waste water in an experimental study using human coronavirus 229E, suggesting low survivability in waste water.[643] Samples taken from the treated sewage outlets of a number of COVID-19 Chinese hospitals were negative.[644, 645] Samples taken (with varying methodology) from external water treatment plants in the UK, Netherlands, France, Spain, the US, and Canada) tested positive in line with the detection of cases in the population which suggests that RT-PCR analysis of sewage could be a potential surveillance tool.[646-654] Testing of sewage treatment works is now being carried out by the Scottish Environment Protection Agency (SEPA) to determine if such data exists to generate a surveillance system. A report prepared for SAGE in November 2020 and April 2021, advised that UK wastewater surveillance programs for COVID-19 have been in place across England, Scotland and Wales since early summer 2020 and is a reliable, timely and cost-effective surveillance method, particularly during low prevalence, and to identify local variants.[655, 656] An analysis of wastewater collected from 6 large urban wastewater treatment plants in England and Wales demonstrated that SARS-CoV-2 RNA is readily detected in wastewater influent across a range of concentrations (from $<1.2 \times 10^3$ to 1.5×10^4 genome copies 100 mL^{-1}).[657] Additionally, levels of SARS-CoV-2 and the genetic variants of the virus observed in wastewater generally correlated with clinical COVID-19 cases within the community.[657] In Orkney (population equivalent 7750 in the catchment area), virus was detected in the wastewater where less than 10 positive cases had been recorded.[655] Wastewater sampling in Switzerland identified the presence of mutations indicative of the new UK variant B.1.1.7 in early December 2020 prior to detection of the first clinical sample in Switzerland.[658] In Canada, it was found retrospectively that wastewater sampling accurately predicted a surge in community cases 48 hrs prior to their detection.[654] There is currently no evidence that COVID-19 is transmitted from sewage/grey water or contaminated drinking water.[655, 659]

Conclusion:

- Due to the uncertainty regarding the environmental survivability of SARS-CoV-2 in real-life conditions, it is essential that the environment is clutter free and frequency of routine cleaning is increased, particularly frequently-touched surfaces.

8. Environmental decontamination

Evidence for cleaning of the care environment for COVID-19 is limited; studies that evaluate the susceptibility of coronaviruses to cleaning/disinfectant products differ by their methodology and often use animal coronaviruses in experimental conditions.[141, 603, 626] An experimental study using a SARS-CoV isolate, tested three different surface disinfectants but all required over 30 minutes exposure time to inactivate the virus to levels below detection.[603] Limited evidence suggests that coronaviruses are susceptible to chlorine-based disinfectants and ethanol-based antiseptics.[626, 660, 661] Kampf et al summarised the efficacy of various disinfectants against both human and animal coronaviruses and found that a concentration of 0.1% sodium hypochlorite was effective in 1 minute and, for the disinfection of small surfaces, 62-71% ethanol revealed a similar efficacy.[626] Laboratory analysis has shown that SARS-CoV-2 can be inactivated in vitro in under 1 minute using 1000mg/L available chlorine.[662] Experimental testing has shown SARS-CoV-2 on inanimate surfaces (stainless steel, plastic, glass, PVC, cardboard) can be inactivated by 70% ethanol, 70% isopropanol, and 0.1% hydrogen peroxide.[661] Specifically, complete inactivation was observed in 30 seconds with ethanol and isopropanol, and in 60 seconds with 0.1% hydrogen peroxide; complete viral inactivation on cotton fabric was observed after 30 seconds with 0.1% sodium laureth sulphate, which is a surfactant present in almost all household cleaning/ personal hygiene agents (e.g. dishwashing liquid, hand soaps and shampoos).[661] Ijaz *et al*[663] provided *in vitro* evidence of the efficacy of a range of cleaning agents against SARS-CoV-2 on common high touch surfaces. Testing during this study found that at 20˚C 44% w/w ethanol disinfectant spray was able to inactivate SARS-CoV-2 with a 5 minute contact time. Under the same conditions and contact time 1.9% lactic-acid-based surface cleanser, and 0.45% benzalkonium chloride-cleaner, both produced log reductions >4.0. At 20˚C and a contact time for 1 minute or less 0.12% p-chloro-m-xylenol (PCMX), 2.4% w/w citric acid disinfecting wipes, and 0.25% hydrochloric acid-based toilet cleaner all resulted in log reductions >3.0 (>4 for PCMX and 0.25% hydrochloric acid). All results were similar to those found for the sodium hypochlorite cleaners tested; 0.14% sodium hypochlorite cleaner, and 0.32% sodium hypochlorite bathroom cleaner.[663] Unfortunately there is a paucity of evidence regarding the efficacy of detergents at deactivating SARS-CoV-2, and due to the novel nature of this infectious agent there is an assumption that only disinfectants will be effective. In vitro analysis of a number of laboratory detergents used for biochemical analysis demonstrated some efficacy against SARS-CoV-2 however the detergents were not designed for environmental cleaning.[664] The CDC states that, in addition to physical removal of SARS-CoV-2, surface cleaning is likely to degrade the virus, while surfactants in

cleaners/detergents can disrupt and damage the membrane of an enveloped virus like SARS-CoV-2.[665]

The WHO recommends that, for coronaviruses, commonly used hospital-level disinfectants such as sodium hypochlorite (at a concentration of 0.5%) are effective for cleaning environmental surfaces, and 70% ethanol is suitable for disinfecting small surfaces.[16] A sampling study found that twice daily cleaning of frequently-touched areas using 5000 ppm of sodium dichloroisocyanurate (a source of free chlorine) resulted in negative swab results for COVID-19 in isolation rooms that had just been cleaned; samples taken from rooms prior to cleaning had multiple positive samples from frequently-touched areas.[604] Similar results were reported from a Chinese hospital in which surfaces were routinely wiped with 1000 mg/L chlorine-containing disinfectant every 4 hours in isolation ICUs and every 8 hours in general isolation wards; none of the environmental samples in these areas tested positive for SARS-CoV-2 contamination.[644] Negative results were also found from sampling of 90 surfaces following disinfection in a Wuhan hospital dedicated to treating COVID-19 patients, in which a comprehensive environmental decontamination protocol was implemented.[385] It consisted of chlorine dioxide air disinfection 4 times a day for 2 hours at a time in COVID-19 wards, irradiation of empty wards with UV light once per day for 1 hour, ultra-low volume spraying of chlorine dioxide (500mg/L) for air disinfection in public areas, and surfaces/objects were 'wrapped' with chlorine-containing disinfection solution (1000mg/L) twice a day.

For situations where health and care settings are at capacity and/or have no breaks in admissions or bed occupancy, the opportunity to conduct a terminal clean or a deep clean may be limited. Solutions to this may include modification to the deep clean regime to allow as high a level of decontamination to be carried out during constant occupancy as possible.

In light of the concern raised regarding aerosol transmission following the identification of positive air samples from hospital rooms,[42, 44, 62, 604, 666] alternative decontamination techniques that offer air decontamination should be explored. Air disinfection using ultraviolet-C light, termed ultraviolet germicidal irradiation (UVGI) is accomplished via several methods: irradiating the upper-room air only, irradiating the full room (when the room is not occupied or protective clothing is worn), and irradiating air as it passes through enclosed air-circulation and heating, ventilation, and air-conditioning (HVAC) systems.[667] UVGI is also used in self-contained room air disinfection units. The overarching limitation of most UVGI systems is that the room must be vacated whilst disinfection is taking place; any reductions in aerosol/surface contamination will be short-lived as once the room is re-occupied, potentially infectious viral particles may again be circulating. UVGI air decontamination should therefore not be used as a replacement for

optimum ventilation provision, however it may have a future use for terminal decontamination and/or in rooms in which AGPs are carried out where improvements to the existing ventilation provision are not possible. One before/after observational study that tested a UVC robot within an American long term care facility had respiratory system infection rates as an outcome measure however the methodological limitations meant that causation could not be proven; there was no certainty that the observed respiratory system infection rate decreases were due to the UVC treatment alone (and not in part due to the manual cleaning that preceded the UCGI treatment).[668] A number of experimental studies have tested the efficacy of UVGI (specifically UVC) at inactivating SARS-CoV-2;[635, 669-675] all of the experimental studies reported on surface decontamination, none of the studies assessed air decontamination. It was not possible to summarise the collective findings of these studies due to the heterogeneity in methodology; the dose of UV, duration of exposure, and distance between the lamp and test isolate varied. Individually, these studies demonstrated efficacy under their varying experimental conditions. In one study, a dose of 1.8mW/cm2 UVC was effective at inactivating experimentally contaminated glass, plastic and gauze.[675] Another *in vitro* study reported a 10-minute exposure (34.9 mJ/cm2) on glass and plastic, and 15 minutes (52.5 mJ/cm2) on stainless steel was required to lower viral titre to below the level of detection [669] Further research into UVC decontamination of SARS-CoV-2 is warranted in real-life trials. A review of UV decontamination technology by HPS recommended that UV light systems can be used as an additional measure when performing terminal room decontamination.[676] However, as surface cleaning is required prior to UVC disinfection, UVC technology will not offer any time-saving benefits and can only be seen as an adjunct to standard environmental decontamination.

The latest version of the PHE IPC guidance advises that low risk (green) COVID-19 pathways can revert to general purpose detergents for routine cleaning, as opposed to widespread use of disinfectants.[587] The Scottish COVID-19 addendum further advises that the use of general purpose detergent for cleaning in the low risk pathway is sufficient with the exception of isolation/cohort areas where patients with a known or suspected infectious agent are being nursed.[419] This was extended to the medium risk (amber) pathway in June 2021.

Conclusion:

- Frequency of environmental cleaning/decontamination in the high and low risk pathways should be increased to at least twice daily, focusing on frequently-touched areas.

- A general purpose detergent should be used for routine cleaning in low risk (green) and medium risk (amber) pathways.

- A combined detergent/disinfectant solution at a dilution of 1,000 parts per million available chlorine (ppm available chlorine (av.cl.)) should be used for transmission-based environmental decontamination as per the NIPCM, in high-risk COVID-19 pathways and any settings experiencing cases/outbreaks. Small surfaces, and those which cannot be cleaned by chlorine-based agents, can be disinfected with 70% ethanol.

- Where terminal cleaning cannot be carried out due to constant occupancy, a modified enhanced clean should be carried out where possible.

- Further research is required to determine the effectiveness of UVC technology for decontamination of SARS-CoV-2.

9. Areas for further research

An overarching limitation of all identified evidence is the novel nature of SARS-CoV-2 and the limited ability for robust research at the early stages of an outbreak.

More work is needed to improve and develop culture techniques to allow determination of the viability of viral particles detected in clinical and environmental samples. This will assist with determination of the infectious dose and will provide insight into the duration of infectivity, particularly in relation to the prolonged viral shedding that is observed in respiratory and faecal samples.

Of particular importance is the need to undertake further research to determine the potential contribution of aerosol transmission of respiratory viruses (not limited to SARS-CoV-2), acknowledging a spectrum of particle sizes, which is understandably beyond the scope of a rapid review.

Further research is required to determine the extent of atypical presentations, pre-symptomatic, and asymptomatic transmission and the overall impact of these on transmission. A robust epidemiological evidence base will assist with the development of infection control measures that are targeted and evidence-based.

Assessment of the efficacy of UVGI and other novel decontamination technologies for environmental decontamination and for the decontamination of PPE would inform COVID-19 IPC guidance and provide reassurance for health and care workers. Studies investigating the efficacy of detergents for environmental cleaning would provide a clear evidence base to support a move away from chlorine-based disinfection in the medium risk pathway.

10. Limitations

An overarching limitation of all identified evidence is the novel nature of SARS-CoV-2 and the limited ability for robust research during a pandemic. Most papers highlight the need for further research.

There are a number of inherent limitations related to rapid reviews, including risk of publication bias, potential omission of key evidence, and the provision of a descriptive analysis of evidence rather than a qualitative analysis. There is a risk of duplication of reported cases as case reports become part of a larger body of evidence.

Consequently, conclusions from this rapid review should be interpreted with caution and considered alongside additional streams of evidence (for example local epidemiological data.

Appendix 1 – Search strategies

Search Strategies used for academic databases.

The search terms for searches conducted from 5th March 2020 until 14th September 2020 were as follows:

1. COVID-19.mp.
2. SARS-CoV-2.mp.
3. 2019-nCoV.mp.
4. novel coronavirus.mp.
5. exp coronavirus/
6. 1 or 2 or 3 or 4 or 5
7. exp infection control/
8. exp disinfection/
9. exp decontamination/
10. exp personal protective equipment/
11. surgical mask?.mp.
12. hand hygiene.mp.
13. clean*.mp.
14. transmission.mp.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
16. 6 and 16
17. limit 17 to English language
18. limit 18 to yr="2020 -Current"

Search terms for 21st September 2020 until 22nd February 2021 were as follows:

1. (coronavirus or corona virus or ncov* or covid* or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19).mp.
2. infection control.ti,kw,ab.
3. disinfection.ti,kw,ab.
4. decontamination.ti,kw,ab.
5. personal protective equipment.ti,kw,ab.
6. ppe.ti,kw,ab.
7. surgical mask*.ti,kw,ab.
8. respiratory protective device*.ti,kw,ab.
9. respirator.ti,kw,ab.
10. FFP3.ti,kw,ab.
11. eye protective device*.ti,kw,ab.
12. goggles.ti,kw,ab.
13. face shield*.ti,kw,ab.
14. visor*.ti,kw,ab.
15. safety glasses.ti,kw,ab.
16. hand hygiene.ti,kw,ab.
17. clean*.ti,kw,ab.
18. transmission.ti,kw,ab.[1]
19. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 1 and 19
21. limit 20 to english language
22. limit to human
23. limit 22 to dd=_____-_____[2]

Search terms for 1st March 2021 onwards were as follows:

1. (coronavirus or corona virus or ncov* or covid* or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19).mp.
2. infection control.ti,kw,ab.
3. disinfection.ti,kw,ab.
4. decontamination.ti,kw,ab.
5. personal protective equipment.ti,kw,ab.
6. ppe.ti,kw,ab.
7. surgical mask*.ti,kw,ab.
8. respiratory protective device*.ti,kw,ab.
9. respirator.ti,kw,ab.
10. respirators.ti,kw,ab.
11. FFP3*.ti,kw,ab.
12. eye protective device*.ti,kw,ab.
13. goggles.ti,kw,ab.
14. face shield*.ti,kw,ab.
15. visor*.ti,kw,ab.
16. safety glasses.ti,kw,ab.
17. hand hygiene.ti,kw,ab.
18. clean*.ti,kw,ab.
19. transmission.ti,kw,ab.
20. airborn*.ti,kw,ab.

21. aerosol*.ti,kw,ab.[2]
22. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 1 and 20
24. limit 21 to english language
25. limit 22 to dd= _____ - _____[3]

Search strategy used for pre-print database.

"infection control" OR disinfection OR decontamination OR "personal protective equipment" OR ppe OR "surgical mask" OR "respiratory protective device" OR respirator OR respirators OR FFP3 OR "eye protective device" OR goggles OR "face shield" OR visor OR "safety glasses" OR "hand hygiene" OR clean* OR "transmission" OR airborn* OR aerosol*

Date limited to previous week.

[2] Search areas adjusted to ".ti,kf,ab." for search on Medline

[3] Date limit term changed to "dt=" for search on Medline

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