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PRACTICE POINTER

Immunity and infectivity in covid-19

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What you need to know

- The risk of SARS-CoV-2 transmission is greatest just before symptom onset and in the early symptomatic period
- There is no surrogate marker to determine infectiousness: PCR positivity overestimates the duration of infectivity and can lead to negative consequences such as delayed surgery, delayed access to health care, and blocking of healthcare systems; culture is not practical; and negative lateral flow tests do not equate exactly with non-infectiousness
- Decisions related to transmission risk must take into account all relevant factors, including the overall risk of infection in the community, the individual's ability to comply with prevention measures, their home and work environment, and the risk profile of their likely future close contacts

Understanding how to assess and communicate risk of transmission and immunity against SARS-CoV-2 is important for all healthcare workers. The evolving evidence base regarding infectivity, risk of transmission, risk of reinfection (dependent on circulating variants), and immunity (influenced by post-infection and post-vaccination waning immunity) can make this very challenging.

There are several reasons why individuals with covid-19 and those caring for them are interested to understand whether they are still infectious:

- Individual concern about passing on infection to others
- Healthcare workers to make risk assessment before patient discharge or interventions
- Policy makers to provide risk reduction recommendations.

This article reviews core underlying principles and explains how interpretation of laboratory data—including polymerase chain reaction (PCR), antigen based lateral flow device (LFD), and antibody testing—can support discussions.

When is an individual non-infectious?

There are insufficient data to precisely delineate when an individual is no longer infectious, and the risk is a continuum with considerable inter-person variability. Individual risk assessments will probably always be required (box 1) and will need to take into account the general risk of infection in the community, including risks posed by new variants (box 2).

Box 1: What to consider when a patient asks if they are still infectious

- The reason for the question—Explore the patient's concerns and the specific nature of the inquiry
- The consequences of labelling the individual as "infectious" (psychological, staffing levels, delayed discharge, delayed surgery, etc)
- The consequences of not regarding the individual as potentially infectious
- The risk from this individual relative to the wider community risk
- The results of tests such as PCR, antigen, and antibody (surrogate markers only)
- Discuss infectiousness in terms of levels of risk
- Advise on measures to mitigate that risk (such as cough hygiene, social distancing, mask/face covering (different grades of mask offer different levels of protection), eye protection, hand hygiene)
- Advise that, although patients may have lingering symptoms after infection that are troublesome, these are not indicative of ongoing infection or ongoing infectiousness

Box 2: Example of an individual risk assessment of infectiousness

An immunocompetent individual who had mild disease and has now recovered after seven days asks you when they will no longer be infectious. They work in retail, sing in a choir, and are the main carer of an elderly relative, for whom they do not have a reliable alternative carer. They are worried about passing on infection to their work colleagues, friends in the choir, and their elderly relative.

Advice for the patient

- We do not have an exact cut-off point for when someone is no longer infectious. However, in one study of people with mild disease no transmissions occurred five days after the onset of symptoms. Analysis of other data has led scientists to conclude that transmission after 10 days is extremely unlikely.
- You can definitely return to your job in retail after 10 days, as per government advice. You are extremely unlikely to be infectious. You are in fact much less of a risk than other people who haven't had the virus yet as, if they get infected, they may be unaware but be in the most infectious stage, which happens early on.
- Even though you are very unlikely to be infectious, you might want to delay returning to the choir, perhaps until after three weeks. This is simply because you can avoid the choir without any significant detriment to anybody, singing is known to increase the risk of transmission, and even though transmission after day 10 is extremely unlikely, the longer the interval since the time of infection the lower the risk. The virus has been cultured in one immunocompetent individual 18 days after symptom

onset, which is why I have suggested three weeks. Similarly, you may decide to delay visiting elderly or vulnerable family members who you don't need to visit because of the very small potential risk.

- However, you are the main carer of one elderly relative, and it is important that you can visit them because there is a risk of harm if you are not able to look after them. You can resume caring for them, as you are extremely unlikely to be infectious at this stage. I would suggest that you pay careful attention to the various preventive measures (social distancing, mask wearing, and hand hygiene) as an additional precaution.

Individuals are most infectious in the early stages of the illness, immediately before and shortly after the onset of symptoms.[1] Interventions that target this highest risk period (such as identification and behavioural modification of individuals with early disease) are likely to have the biggest impact in controlling transmission overall. Infectivity and viral load decline from the onset of symptoms.[1 2] In one study, no transmissions occurred after day five of symptoms even in household contacts.[3] In mild to moderate cases, individuals are considered highly unlikely to be infectious beyond 10 days.[4 5] Over-emphasis on the latter stages of recovery (for example, demonstrating PCR negativity in recovering patients) is unlikely to have a significant impact on transmission and can lead to negative unintended consequences, such as delayed surgery, delayed access to health care, and blocking of healthcare systems. It may still have a place in certain circumstances (for example, among immunocompromised patients).

Guidelines worldwide provide recommendations on when it is safe to return to work, broadly based on the likely infectious period.[6-11] These guidelines continue to evolve and can be referenced for up-to-date information. There is no longer a legal requirement in the UK for someone who has covid-19 to self isolate, although it is still recommended.[12] In Wales healthcare workers are advised to self isolate and to return to work when they have two negative lateral flow test results taken 24 hours apart, starting five days after the date of their initial positive test. Those who continue to test positive are advised to continue testing up to day 10. If they are still positive at that point, they are considered unlikely to still be infectious and they can return to work providing they are medically fit.[9]

Patients in hospital are typically kept in isolation for 10 days from the onset of symptoms (14 days for those who are severely immunocompromised); they are then able to stop isolating providing that they have been afebrile for 48 hours and all their symptoms (except for cough and anosmia) have resolved. This can be reduced if they meet these clinical criteria and have two negative lateral flow test results taken 24 hours apart, starting six days after the date of their initial test.[10]

International travel and schools are other areas where transmission risk has been scrutinised. In the case of international travel the concern is primarily related to spread of infectious variants with varying degrees of ability to infect vaccinated individuals. There is still potential for global spread of a more virulent variant of SARS-CoV-2. However, the omicron wave has largely tempered those fears for now. In addition, attempts to prevent infiltration of variants through travel restrictions have to date been largely unsuccessful apart from in countries where very strict travel restrictions are put in place before any threat of introduction of the new variant (for example, New Zealand). Risks of transmission in schools need to be balanced against the negative impact on children's mental wellbeing and education, particularly given that most children are at low risk of complications from covid-19.

Are all individuals equally infectious?

Individuals are not equally infectious. Onward transmission varies according to specific host and contact factors and the nature of the exposure (box 3). Transmission is primarily related to direct contact with an infected individual. In one study, transmission rates on trains were highest in those in adjacent seats (attack rate 3.5% (range 0 to 10.3%)) and increased with time (0.15% per hour) and proximity.[13] Transmission in passengers who immediately occupied a positive individual's vacated seat occurred in only one out of 1342 cases (0.075%).[13] Household contacts (11.8%) are more likely than non-household contacts (1.2%) to develop disease.[14]

Box 3: Factors associated with increased risk of transmission

Environment

- Indoors
- Poor ventilation
- Crowding
- Close proximity (roughly <2 metres, but transmission is a continuum, the further away the better)
- Shared facilities
- Cold ambient temperature
- Low humidity

Host factors

- Recently infected (highest risk around the time of symptom onset)
- High viral loads
- Severe disease (risk ratios 3.76 (95% CI 1.1 to 12.76) and 3.99 (1.00 to 15.84) for severe pneumonia and acute respiratory distress syndrome/sepsis[3])
- Age
- Comorbidity
- Immunocompromised

Behavioural

- Singing, shouting, chanting
- Coughing and poor cough etiquette
- Sneezing
- Hugging, kissing
- Mask etiquette
- Hand hygiene
- Aerosol generating procedure
- Duration of contact

Viral factors

- Changes in the viral genome have been linked to increased transmissibility (for example, D614G and variant of concern VOC-202012/01, both of which have changes in the spike protein)

Investigations of outbreaks have demonstrated very high attack rates in specific settings.[15-17] These large scale, "super-spreader" events,[15-17] are characterised by explosive early growth and sustained transmission in later stages,[18] with 20% of infected individuals triggering 80% of all infections.[19] As transmission is unpredictable and random in nature (stochastic), exercise caution to not over-interpret data from small groups.[20]

What other factors affect the risk of transmission?

Transmission is influenced by external factors, which should be considered as part of any assessment (box 3):

- Prevention measures—masks,[21] social distancing, vaccination status, hand hygiene, etc
- The activity being undertaken (such as choir)
- The environment (higher risk in crowded or shared facilities and if ventilation is poor)
- The susceptibility and risk of severe disease among contacts.

Individuals are most infectious just before and just after symptom onset. Infectivity decreases thereafter, with transmission after day 10 considered extremely unlikely following mild or moderate disease. Immunocompromised people and those with severe disease are likely to be infectious for a longer, undefined period. Resolution of symptoms is reassuring, signifying development of immunity with likely reduced risk of transmission. Other preventive measures (hand hygiene, mask wearing, social distancing) reduce residual risk further.

What surrogate markers are used to decide on infectivity?

There is currently no ideal surrogate marker for infectiousness (table 1). Viral culture is not a routinely available test in most settings. PCR overestimates the duration of infectiousness but can underestimate risk by virtue of false negative results. Lateral flow devices (LFDs) identify the most infectious individuals reliably but don't detect all infectious individuals. LFDs do not have the same issues of residual positivity as PCR.

Table 1 | Surrogate markers of infectiousness

	Pros	Cons	Overestimate infectivity	Underestimate infectivity	Limits of detection after symptom onset
Culture	• Confirms presence of intact, viable and potentially infectious virus • Surrogate for infectivity	• Requires category 3 or 4 laboratory • Not routinely available • Difficult to perform	• Virus deposited into a favourable environment	• Use of a cell line rather than a natural host • Delay in inoculation (death of virus in transit)	• Maximum time 119 days (in an immunocompromised individual)[22 23] • For mild disease 8 days[24 25] • For severe disease 111 days[26]
PCR	• Virus can be inactivated before processing • Requires category 2 laboratory • Widely available • Fast turnaround time • Sensitive • Provides a semi-quantitative result	• Will detect viral fragments and/or dead RNA	• Detects viral fragments and/or dead RNA • False positive rate unknown – estimate 0.8-4.0%[27]	• False negative rate ~10-30%	• Maximum time 156 days[22 28 30] • Median time to a negative upper respiratory tract test 14.5-24 days[30 31]
Lateral flow test	• Point of care test: results within 20 minutes • Can be taken regularly • Minimally invasive options available • No transport, laboratory infrastructure, validation, or communication of results required • Less sensitive than PCR and less likely to overestimate infectivity	• Inter-user variability • False positive results (persistent in some individuals) • Lower sensitivity than PCR, may underestimate infectivity	• Detects viral antigen • False positive rate varies according to test being used – range 0-7.6%[32]	• Lower sensitivity than PCR • False negative rate relative to PCR ~65-89%	• Not known

Culture

Most recommendations are based on viral PCR and culture (table 1). Viral culture confirms the presence of intact, viable, and potentially infectious virus. Although the circumstances required for viral culture are not the same as for transmission, it is considered a reasonable surrogate. In immunocompetent individuals, positive culture beyond day 10 in patients with mild disease is uncommon.[4] It is more common in those with severe disease.[26 33-35] Virus has been detected up to day 18 in mild disease,[24 25] day 111 in severe disease,[26] and day 119 in an immunocompromised individual.[22 23] Individuals may not be very infectious even when culturable virus is present. One individual with severe infection who was culture-positive at day 111 did not cause any secondary infections despite quarantine termination at three months.[26] Also, no infections occurred in 852 contacts exposed to individuals with mild disease after day five.[3]

Polymerase chain reaction (PCR)

PCR detects the presence of SARS-CoV-2 viral RNA. Previously, guidelines advocated use of PCR as a surrogate for non-infectiousness but studies on viral dynamics have shown that there are several reasons why this is not appropriate.

- PCR can detect non-viable virus and overestimates the duration of infectivity,[3 28 29 31] with one surveillance study reporting no secondary cases among 790 contacts of 285 "persistently positive" people.[36] Relying on PCR as a measure of non-infectiousness may prolong hospital admission and isolation unnecessarily.[30]
- Results can fluctuate from positive to negative at all stages of infection, can become positive again even after two consecutive negative tests,[23 37 38] can be detected for longer in those with severe infection,[22 39] and may fluctuate at the level of detection for several weeks.[40]
- Results vary according to sample site (lower respiratory tract samples remaining positive for longer).[38]

- False negative results can provide false reassurance.[31]

Results can be semi-quantified by the number of cycles required to reach the predetermined positive threshold—the cycle threshold (CT). Low CT values indicate high viral loads (strong positive <25); high CT values (>35) may indicate low viral loads (weak positive). Weak positive results are most common in the very early and late stages of infection but may also be false positives.[41] The CT value is probably linked to infectiousness[30 42]; supported by decreased ability to culture the virus as the CT value increases[4 5 25 33 42] and as found with other diseases.[43] The CT value is affected by some external factors, such as swab quality and disease stage (lower in early disease but may be rising), so results need to be interpreted with caution.

Lateral flow devices (LFDs)

LFD antigen tests detect a protein antigen which forms part of the viral wall. When present, it is indicative of ongoing replication and therefore the presence of infectious virus. Comparative studies have shown that it is less sensitive than PCR, detecting around 65-89% of PCR-positive samples.[44] However, the sensitivity is higher in those with higher viral loads (96% for >1 000 000 copies per mL, 92% for 10 000–1 000 000 copies per mL, and 43% for <10 000 copies per mL[45]) and those who were culture positive (>95%).[44] It has been estimated that LFD tests would detect 83-89% of cases with PCR-positive contacts.[46] The rapid turnaround time and practicality of lateral flow tests mean they provide a reasonable testing strategy for reducing infection risk in certain circumstances—such as when PCR testing is not practical, when the consequences of a false negative result are acceptable, and when the balance of risks (immediate LFD result *v* delayed PCR result) favours their use.

When are individuals considered to be immune?

Individuals are understandably keen to know whether they are susceptible to reinfection. Reinfection with phylogenetically distinct variants of SARS-CoV-2 has been reported after as little as 48 days[47] in an otherwise healthy 25 year old man. Asymptomatic reinfection (PCR positivity)[48 49] and infection with milder disease[50 51] and more severe disease[47 51] have all been described. Over time, infection and reinfection have resulted in milder disease at the population level, which is probably related to improved immunity combined with reduced virulence of emerging strains. Reinfection is more likely to be established in individuals with symptoms and more severe disease. The risk of reinfection is a function of the level of immunity present and the infecting viral strain (for example, vaccine escape variants), which is in turn dependent on the strain(s) circulating in the community at that time. Immunity decreases with time from infection or vaccination. Reinfection is more likely when a new strain emerges, particularly if that strain has properties that enable it to evade immunity developed from previous infection or vaccination. An example of this was seen with the rapid spread of the omicron variant in late 2021.

What factors can you discuss when asked by a patient if they are immune?

- What is known about the response to SARS-CoV-2 (i.e. immunity lasts at least 90 days and likely longer in most people)
- The different types of immunity (T cell and antibody)
- That current tests are only surrogate markers for immunity and do not take account of immune memory
- Reinfections can occur
- Reinfections are often milder than the first episode
- Recovered individuals should comply with prevention measures to avoid reinfection

Most people will be protected from symptomatic reinfection for at least five months, and the immediate risk of reinfection is low (0.02%, incidence rate 0.36 per 10 000 person weeks).[52 53] There is evidence of increased protection from infection in individuals who are vaccinated after a primary infection, with one prospective cohort study showing that infection-acquired immunity waned after one year in unvaccinated participants but remained consistently higher than 90% in those who were subsequently vaccinated, even in people infected more than 18 months previously.[54]

Immunity in coronavirus infections

Evidence from infections with other coronaviruses (seasonal coronaviruses, MERS-CoV, SARS-CoV-1) and surrogate markers of immunity (antibody and T cell responses) can help inform our understanding of immunity in SARS-CoV-2

Seasonal coronavirus

Serological studies from the 1960s suggest cycling of infection, with different coronavirus strains predominating every two to four years.[55] Re-challenge experiments (table 2) suggest complete immunity from symptomatic reinfection for at least one year if "reinfected" with the same strain, but only partial immunity when exposed to a heterologous strain.[56 57] Short duration asymptomatic shedding is possible following re-challenge with the same strain.[60]

Table 2 | Coronavirus re-challenge experiments

Study	Subject	Strain	Time between exposure	No of participants	Antibody positive before re-challenge	Outcome
Reed 1984[56]*	Human	Identical	8-12 months	6	5/6	6/6 completely immune
		Heterologous	12 months	12	—	7/12 developed cold symptoms 8/12 shed virus for a short period, including one asymptomatic
Callow 1990[57]†	Human	Identical	12 months	9	7/9	No clinical symptoms 6/9 shed virus for a short period
Chandrashekar 2020[58]	Rhesus monkeys	SARS-CoV-2	35 days	9	9/9 neutralising antibodies. Boosted on re-challenge in all	Limited RNA in BAL of 3/9 Low levels of sub-genomic messenger RNA in 4/9
Corbett 2020[59]	Rhesus monkeys vaccinated	SARS-CoV-2	4 weeks after second vaccine	8 low dose 7 high dose	15/15 neutralising antibodies	15/15 reduced lung infection Reduced shedding, particularly in high dose group

*Full immunity to the same strain lasts at least one year but only partial immunity is present when exposed to a heterologous strain.56

†Some short duration asymptomatic shedding possible on re-challenge/reinfection.57

Immunity to seasonal coronavirus is not lifelong.[60] Most children are seropositive for seasonal coronavirus by age 3.5 years, yet seasonal coronavirus infections account for ~25% of acute respiratory illness into adulthood.[60]

SARS-CoV-2

Data on immune response to infection and vaccination is continuing to evolve. Presence of antibody is not proof of immunity. Neutralising antibody tests are considered most predictive of protection but are not available routinely. Neutralising antibodies develop in most infected individuals (>90%),[61] although in some the levels are very low or absent,[62] suggesting that other elements of the immune system are driving recovery.

Antibody responses are stronger and last longer after severe infection.[63] Given the protective nature of antibodies in seasonal coronavirus infection, we might expect protection against the same strain to last for most people for at least 12 months. However, viral evolution may be more frequent and common in the early phases of the pandemic, and immunity akin to that seen in studies of seasonal coronavirus in adults may take time to develop.

There are currently four approved vaccines in the UK[64] and more available worldwide. Data from vaccination studies show that protection wanes over time but lasts in most people for at least four months.[65] Pfizer vaccine was effective against symptomatic disease in 96% up to two months, 90% for two to four months, and 84% for four to six months. Protective efficacy of the vaccine from symptomatic disease varies according to viral strain and patient age in the range of 70%[66] to 95%.[65] Protection against severe infection, hospitalisation, and death is higher still. At the time of writing vaccination has proved effective against all naturally circulating strains. Evidence regarding the efficacy against the latest variant (omicron) is continuing to emerge, although protection is definitely reduced.[67] Immunity derived from vaccination declines over time. In recognition of this, the UK Joint Committee on Vaccination and Immunisation has recommended a fourth vaccine dose (Spring booster approximately six months after the previous dose) for those at higher risk of covid-19. This will likely be repeated in the autumn. Decisions on booster vaccinations for the general population will be made in response to evolving evidence.

In summary, infection with coronaviruses do not result in lifelong immunity, and reinfection is common. The natural course for coronavirus infection includes repeat exposure and repeat infection over a variable time course. Over time, SARS-CoV-2 will likely transform into a seasonal coronavirus infection. With the development of increased immunity the risk of re-exposure and reinfection will decline, and the period between episodes will likely increase.

Patient's perspective: Uncertainty about immunity

When I discovered I had covid-19, I had numerous symptoms and remained unwell for a protracted period. The symptoms lifted suddenly after five and a half months when I woke up feeling better.

When I started to go out, I was extremely cautious despite it being weeks since the onset of my symptoms. I was conscious of not touching any walls—what if an elderly person touched the same wall hours later, caught the virus from me, and died? If someone walked down the street, I gave them a wide berth. I questioned whether it was irresponsible of me to leave the house for a walk on my road—I checked and double-checked the guidance.

I still have mixed feelings about how information on immunity affects my decision making. It is now six months since the onset of my symptoms. Part of my confidence in visiting vulnerable relatives comes from a sense that I am less likely to pass covid on to them unknowingly because I am less likely to get infected again. But then I worry about reinfections—what if I get covid again but have very few symptoms and unknowingly spread it? The uncertainty about immunity makes some decision making hard—who to see and when. What happens when our immunity runs out? And will I ever know when this happens? I do not feel that having had covid removes much of this uncertainty. It hasn't really added much confidence for me, as I still have so many unanswered questions.

Additional educational resources

Centers for Disease Control and Prevention

- COVID-19: Ending isolation and precautions for people with COVID-19: interim guidance. 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html
- COVID-19: Interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 (COVID-19) pandemic. 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html
- Interim guidance for managing healthcare personnel with SARS-CoV-2 infection or exposure to SARS-CoV-2. 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html

European Centre for Disease Prevention and Control

- Guidance on ending the isolation period for people with COVID-19–third update. 2022. https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation
- Contact tracing in the European Union: public health management of persons, including healthcare workers, who have had contact with covid-19 cases – fourth update. 2021. https://www.ecdc.europa.eu/en/covid-19-contact-tracing-public-health-management

UK Health Security Agency

- COVID-19: the green book, chapter 14a. Coronavirus (COVID-19) vaccination information for public health professionals. 2022. https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a

Information resources for patients

UK Health Security Agency

- Coronavirus (COVID-19): guidance for the public. 2022. https://www.gov.uk/government/collections/coronavirus-covid-19-list-of-guidance#guidance-for-the-public
- Coronavirus (COVID-19): antibody testing. 2022. https://www.gov.uk/government/publications/coronavirus-covid-19-antibody-tests/coronavirus-covid-19-antibody-tests
- COVID-19: guidance on protecting people defined on medical grounds as extremely vulnerable. 2022. https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19

NHS

- Changes to testing for coronavirus (COVID-19). 2022. https://www.nhs.uk/conditions/coronavirus-covid-19/testing/get-tested-for-coronavirus/
- National infection prevention and control manual for England. 2022. https://www.england.nhs.uk/publication/national-infection-prevention-and-control/

Questions for future research

- How long are individuals with covid-19, particularly those infected with new strains, infectious for?
- Is there a reliable surrogate marker for infectiousness?
- Can the cycle threshold (CT) value of PCR tests (or quantitative PCR) be used to predict non-infectiousness?
- How are lateral flow and PCR tests best deployed to aid risk decision making?
- Is there a reliable surrogate marker for immunity that predicts protection from reinfection or significant illness?

Education into practice

- How would you discuss the uncertainty around immunity with your patients?
- How do you use viral detection tests (PCR, lateral flow, and other viral antigen tests) when discussing risk of transmission with patients?
- Reflect on a recent case of covid-19 where the individual was worried about onward transmission or duration of immunity? Would you do anything differently having read this article?

How this article was created

This article was assembled using the expertise of the writing group to appraise the key parts of evidence in each heading. A targeted Medline search was carried out for SARS-CoV-2 culture on 5 December 2021. It yielded 3793 results. Titles were screened for papers that discussed culture of SARS-Co-V-2. Relevant abstracts were reviewed, and full articles reviewed where appropriate. Three review articles with more extensive search criteria were scrutinised for data relevant to this article. The guideline section was constructed after accessing guidelines from major European countries, UKHSA, ECDC, CDC, and WHO on 5 December 2021.

How patients were involved in the creation of this article

The article was reviewed by two patients. Their opinions were used to guide the focus of the article and to respond to main concerns. Also one patient wrote a perspective to highlight the considerations and concerns that a patient may have.

Contributors: BH and CJ produced the article first draft. The article was reviewed, edited, and rewritten by HH (microbiology advice including expertise in compiling guidelines for use in Wales), SL (public health advice including expertise in advising and managing cases in the community and discharge from hospital into the community), and SH (primary care advice).

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