Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Overview of multiplex antigen near-patient tests for acute respiratory infections

31 October 2023

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About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Acknowledgments

HIQA would like to thank all members of the Expert Advisory Group (EAG) listed below who provided their time, advice and information in support of this work.

Membership of the Expert Advisory Group (EAG) involves review of evidence synthesis documents and contribution to a discussion which informs the advice from HIQA to the Minister for Health. It does not necessarily imply agreement with all aspects of the evidence synthesis or the subsequent advice.

The membership of the EAG was as follows:

Dr Colette Bonner	Deputy Chief Medical Officer, Department of Health
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Dr Máirín Ryan (Chair)	Director of Health Technology Assessment & Deputy Chief Executive Officer, HIQA
Dr Susan Spillane	Deputy Director, Health Technology Assessment, HIQA
Dr Scott Walkin	Antimicrobial Resistance and Infection Control Lead, Irish College of General Practitioners

Members of the Evaluation Team

This report was led by staff in HIQA's HTA Directorate. The following individuals contributed to the management, technical writing or dissemination of this report:

Cillian McDowell, Tom Lynch, Carol McLoughlin, Debra Spillane, Louise Larkin, Máirín Ryan, Marie Carrigan, Michelle O'Shea, Michelle O'Neill, Susan Spillane.

Conflicts of interest

Dr Daniel Hare reported participation in the Irish RSV Network Forum, a non-promotional scientific educational meeting organised and sponsored by Sanofi.

Dr Scott Walkin reported that any technologies employed in clinical practice could influence his income.

Key findings and advice to the Minster for Health

Respiratory tract infections (RTIs) are amongst the most common illnesses. Some of the most common RTIs, which account for a large proportion of outbreaks annually, are caused by viruses including SARS-CoV-2, influenza, and respiratory syncytial virus (RSV). These RTIs contribute to a sharp increase in hospital admissions in the winter months and may present with very similar symptoms, making it difficult to clinically differentiate between them.

Both reverse transcription polymerase chain reaction (RT-PCR) based tests and antigen near-patient tests (NPTs; that is, tests performed by a doctor or other healthcare worker close to a patient, as opposed to self-testing by a patient which is out of scope in the current report) can be used to detect a single virus, defined as singleplex tests, or more than one virus, defined as multiplex tests. RT-PCR based tests are the gold standard for identifying respiratory pathogens and are typically conducted in a laboratory setting. Antigen near-patient tests (NPTs) are quicker, cheaper and easier to perform than RT-PCR tests. However, they are generally less accurate. The use of multiplex antigen NPTs may be of interest to detect and manage RTIs in primary and residential care facilities.

Following a request from the Department of Health, HIQA agreed to provide an overview of the evidence on the potential use of multiplex antigen NPTs to detect SARS-CoV-2 and one or both of influenza and RSV in residential and primary care settings.

The key findings of this report, which informed HIQA's advice, were:

- Worldwide, a large number of multiplex antigen NPTs have been commercialised, with a wide variation in the characteristics of these tests.
- One use case of a multiplex antigen NPTs in a community healthcare setting in Ireland was identified. The University College Cork Student Health Department used a multiplex antigen NPT with the capacity to test for SARS-CoV-2, adenovirus, influenza A and B and RSV. However, the student population assessed in this study is not representative of the broader population that would attend primary or residential care facilities. No relevant examples of the use of multiplex antigen NPTs were identified internationally.
- No guidance around the use of multiplex antigen NPTs in Ireland was identified. Two international recommendations were identified.
    - A 2022 joint statement from the Public Health Laboratory Network and Communicable Diseases Network Australia did not recommend the use of multiplex antigen NPTs.

  - A 2023 evaluation report by the Haute Autorité de Santé (HAS) in France found no evidence of clear medical benefit to using multiplex antigen NPTs in primary care settings, although they highlighted the potential for population-level benefits such as a reduction in antibiotic prescription and repeat consultations. However, no evidence demonstrating these benefits was identified in their evaluation.

- Multiplex antigen NPTs are still relatively new technologies and so guidance and or recommendations on their use may not have been considered until recently. Although no planned further guidance and or recommendations were identified, it is plausible that more may be published this year to inform winter 2023/2024 plans.

- As part of the World Health Organization ACT-Accelerator Transition Plan (October 2022 to March 2023), support has been given to the development and acceleration of access to affordable COVID-19 rapid antigen diagnostic tests and to the rollout of point-of-care diagnostics at primary healthcare levels and of multiplex multi-pathogen platforms more generally. Although no guidance around the use of multiplex NPTs was provided, this highlights potential interest in the development of these and related technologies.

- In the current report, one study on the effectiveness of multiplex antigen NPTs in primary and residential care facilities was identified. No studies on the advantages, disadvantages and feasibility of this form of testing were identified.

- Although the manufacturer-reported diagnostic accuracy for multiplex antigen NPTs is generally good, the HAS evaluation report highlighted:

  - the typically very low sensitivity of singleplex antigen NPTs for identification of influenza and RSV.

  - limitations in the data underpinning the manufacturer-reported diagnostic criteria for three tests.

- The available evidence suggests that the sensitivity of these tests may be low, in particular for influenza and RSV, which could limit their utility. Indeed, their utility in primary or residential care settings, for example, in reducing inappropriate antibiotic use or emergency department visits, is unclear. There is a need for studies in primary and residential care settings which prospectively assess the diagnostic performance and clinical utility of multiplex antigen NPTs.

HIQA's advice to the Minister for Health is as follows:

- A large number of multiplex antigen near-patient tests (NPTs), that test for SAR-CoV-2 and one or both of influenza and respiratory syncytial virus (RSV), have been developed since the COVID-19 pandemic.
- Due to a lack of evidence, the effectiveness, advantages, disadvantages and feasibility of using multiplex antigen NPTs in primary and residential care facilities are unclear.
    - Proposed benefits of using multiplex antigen NPTs in primary care and residential care facilities include reducing inappropriate antibiotic use or decreasing emergency department visits for non-serious infections that could be diagnosed at the first consultation. However, the current report identified no evidence demonstrating this.
- Given the uncertainty around the effectiveness (relative to reverse transcription polymerase chain reaction (RT-PCR) tests), and around the advantages, disadvantages and feasibility of use of multiplex antigen NPTs in primary care and residential care facilities, prospective studies are required to inform public policy on the use of multiplex antigen NPTs in these settings.

Plain language summary

Infections in your sinuses, throat, airways or lungs are called respiratory tract infections. The most common respiratory tract infections are caused by viruses such as SARS-CoV-2 (the virus that causes COVID-19), influenza (flu), and respiratory syncytial virus (RSV). The symptoms of these infections are very similar, such as having a dry cough or a fever. This can make it very difficult to know which infection a person has. Diagnosing which infection they have is important for choosing the best treatment and responses, such as deciding if a person should self-isolate. This report looks at using a type of test called a 'multiplex antigen near-patient test (NPT)' to diagnose an infection and identify which virus is causing the infection.

- 'Multiplex' means that the test can look for more than one virus at the same time, for example, they can test for both SARS-CoV-2 and influenza viruses.
- 'Antigen tests' are tests which look for virus proteins in a sample to show which particular virus is present. They can produce a result quickly.
- 'Near-patient tests' are tests performed close to a patient instead of needing to be sent to a laboratory. These are performed by a doctor or other healthcare worker.

The multiplex antigen NPTs considered in this report test for SARS-CoV-2 and one or both of influenza and RSV. This report:

- describes what multiplex antigen NPTs are
- reports on examples of their use and recommendations around their use in Ireland and internationally, and
- reviews research on how accurate the tests are, and what are the potential advantages and disadvantages of using them in primary and residential care facilities (for example, general practice (GP), nursing homes or community mental health facilities).

There was one example found of the use of the tests in Ireland. This involved testing student patients in the University College Cork Student Health Department. No examples were found in other countries. No guidance on using the tests in Ireland was found, but there is some guidance internationally. In June 2022, the Australian Public Health Laboratory Network and Communicable Diseases Network Australia did not recommend the use of multiplex antigen NPTs due to concerns around the accuracy of the tests. In July 2023, the Haute Autorité de Santé (HAS; that is, the French National Authority for Health) also did not recommend the use of multiplex antigen NPTs until more research into how accurate they are is completed. HAS also would like to see more research which investigates the advantages and disadvantages of using multiplex antigen NPTs. As the tests are still quite new, it is possible that other countries might publish guidance later this year.

There is currently very little research into how accurate these particular tests are. There is no research on what the advantages or disadvantages of using these tests are. Understanding the answers to these research questions is important to make sure that the tests do what they are supposed to do, and to make sure that they are useful and lead to better treatment. Until more research is done to help with this understanding, the benefits of using these tests are unclear.

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List of abbreviations used in this report

EAG	expert advisory group
DALY	disability-adjusted life year
HAS	Haute Autorité de Santé
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
IVDR	In Vitro Medical Devices Regulation
LFA	lateral flow immunoassay
NPT	near-patient test
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RT-PCR	reverse transcription polymerase chain reaction
WHO	World Health Organization

1. Introduction

1.1. Background to the request

Respiratory tract infections (RTIs) are among the most common illnesses.[1, 2] RTIs can be caused by a range of pathogens including bacteria, fungi and viruses.[3-6] Some of the most common RTIs, which account for a large proportion of outbreaks annually, include SARS-CoV-2, influenza, and respiratory syncytial virus (RSV).[7-9] Furthermore, these respiratory infections contribute to a sharp increase in hospital admissions in the winter months. These RTIs can present with very similar symptoms, making it difficult to clinically differentiate between them.[10] Differentiating between these respiratory viruses may be important as early treatment with antivirals targeted at the specific infection, is beneficial in individuals at risk of hospitalisation or death as a result of the infection.[11, 12] Additionally, testing for multiple pathogens may be beneficial as positivity for one does not rule out concurrent infection with another, and co-infection by respiratory viruses may be associated with adverse clinical outcomes.[13] Therefore, tests that can rapidly distinguish between SARS-CoV-2, influenza, and RSV may have important implications for patient care. Multiplex antigen near-patient tests (NPTs) can detect multiple virus-specific antigens, and can detect the presence of infection during the acute stage of infection. They typically have a faster turnaround time, are available for self-testing purposes, and are easier to operate relative to the gold standard, reverse transcription polymerase chain reaction (RT-PCR), a laboratory technique that involves identifying DNA or ribonucleic acid from a sample, which requires trained laboratory personnel. However, they are typically less accurate.[14]

Following a request from the Department of Health, HIQA agreed to provide an overview of the evidence on the potential use of multiplex antigen NPTs to detect SARS-CoV-2 and one or both of influenza and RSV in residential and primary care settings. The purpose of Section 1.2 is to outline the process by which HIQA's Health Technology Assessment Directorate conducted this overview.

1.2. Overall approach

The objectives of this report are to provide:

- a description of multiplex antigen NPTs
- an overview of how these tests are used in residential and primary care settings in Ireland and internationally
- an overview of the effectiveness, advantages and disadvantages of using multiplex antigen NPTs in residential and primary care settings.

The purpose of this report is to provide an overview of multiplex antigen NPTs for acute respiratory infections in residential and primary care settings. Therefore, individual tests are not discussed in detail. However, there is some discussion of a number of specific tests that are mentioned frequently in the literature identified.

During the scoping phase of the project, an evaluation report, published in June 2023 by the Haute Autorité de Santé (HAS) in France, on the use of multiplex antigen NPTs for SARS-CoV-2, influenza and RSV "in a city context" (typically during a consultation in a doctor's office) was identified.[15] Relevant findings from the HAS report are summarised in each chapter of the current report, followed by any additional evidence that was identified.

HIQA appointed an Evaluation Team comprising staff from the health technology assessment Directorate to carry out the assessment and convened an Expert Advisory Group (EAG) comprising representation from the Department of Health, patient representatives, and individuals with relevant expertise in diagnostics, microbiology, infectious diseases, public health, residential care and general practice. The role of the EAG was to inform and guide the process, provide expert advice and information, and provide access to data where appropriate. A full list of the membership of the EAG is available in the acknowledgements section of this report.

The Terms of Reference of the EAG were to:

- Contribute to the provision of high quality and considered advice by HIQA to the Minsiter for Health.
- Contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate.
- Be prepared to provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to HIQA regarding the scope of the analysis.
- Support the Evaluation Team led by HIQA during the assessment process by providing expert opinion and access to pertinent data, as appropriate.
- Review the project plan outline and advise on priorities, as required.
- Review the draft report from the Evaluation Team and recommend amendments, as appropriate.

- Contribute to HIQA's development of its approach to health technology assessment by participating in an evaluation of the process on the conclusion of the assessment.
- Notify the project team if a nominee can no longer participate or contribute to the process as non-participation may require alternative EAG membership to be sought.

A draft of the report was prepared by the Evaluation Team and disseminated to the EAG for review prior to their meeting. At the meeting, the draft report was discussed, with amendments made, where appropriate. The completed report will be submitted to the Department of Health, and published on the HIQA website.

2. Description of Technology and Burden of Disease

Key points

- SARS-CoV-2, influenza and respiratory syncytial virus (RSV) are the causative pathogens associated with the majority of respiratory tract infections (RTIs) and outbreaks identified in Ireland. RTIs are responsible for substantial increases in hospital admissions during the winter months. The clinical symptoms from these pathogens are similar, making it difficult for clinicians to differentiate which virus is causing the infection.
- Reverse transcription polymerase chain reaction (RT-PCR) based tests are the gold standard for identifying respiratory pathogens and are typically conducted in a laboratory setting. While samples can be processed in less than two hours, the time from sample collection to provision of results is typically much longer. RT-PCR based tests are highly accurate because they use an amplification process which allows them to detect even small amounts of viral RNA in a sample.
- Antigen NPTs do not include an amplification step and are therefore less able to detect low levels of viral antigens. These tests are quicker to perform than RT-PCR tests and are most accurate when used in symptomatic individuals with a high viral load. Paper-based lateral flow immunoassays (LFAs) are manually read while some antigen tests are used in conjunction with processing devices which interpret and digitally report the results.
- Tests that can detect one pathogen from a sample are known as singleplex tests, whereas tests that allow one sample to be tested for a number of pathogens are known as multiplex tests. There is particular interest in multiplex antigen NPTs that might be able to detect SARS-CoV-2 and influenza A/B and or RSV.
- Worldwide, a large number of multiplex antigen NPTs have been commercialised. Although the examination of specific tests was beyond the scope of the current report, applying the World Health's Organization REASSURED criteria (standard criteria used to assess NPTs) to multiplex antigen NPTs more broadly indicated variation in test characteristics.
  - The 'real time connectivity' varies, as some test results are visually inspected and others display the result using specialised processing devices.
  - The 'ease of specimen collection' varies with multiplex antigen tests using either nasopharyngeal or nasal swabs.

- The 'affordability' of tests varies. Lateral flow immunoassay (LFA) multiplex antigen NPTs may cost approximately €1 to €2, while some multiplex antigen NPTs require a processing device that may cost several thousand euro. Tests which are used in conjunction with these processing devices are typically more expensive (in the range of €10 to €20).
- The 'sensitivity and specificity' of multiplex antigen tests are typically reported as being above 90% by manufacturers, although there are limited validation studies of the performance of the tests to date.
- 'User friendliness' varies across tests. For example, LFAs require only a few steps to take and test the sample, while multiplex antigen tests with processing devices require training to operate.
- Multiplex antigen tests are 'rapid and robust', taking between 5-30 minutes to process a result and can be stored at temperatures between 2-30 °C.
- Paper-based LFAs require no further equipment than the reagent, swab and testing cassette which are typically packaged together. Multiplex antigen tests with processing devices are battery operated.
- 'Deliverable to end users' - LFAs are inexpensive and easy to use to the extent that they can be used for self-testing. Devices that require processing devices are more expensive and require some technical expertise to operate.

2.1. Background

The purpose of this chapter is to provide a background to respiratory pathogens and the associated burden of disease and to describe multiplex antigen near-patient tests (NPTs) as a means to detect respiratory pathogens. Antigen tests are commonly associated with self-testing particularly in the case of SARS-CoV-2. This report is focused on the use of multiplex antigen NPTs, which can detect more than one virus, by a healthcare professional outside of the traditional laboratory environment, generally near to or at the side of the patient. Tests designed for self-testing are out of scope. It is unclear exactly how many different multiplex antigen NPTs have been developed since the COVID-19 pandemic, although a preliminary search of finddx.org indicates that it is in excess of 80. However, this database relies on self-reporting from manufacturers and so the true number may be higher. Furthermore, it is not clear how many of these tests are approved for use in the European market.

2.2. Respiratory pathogens

Respiratory tract infections (RTIs) can be caused by a range of pathogens including bacteria, funguses and viruses[3-6] and often give rise to a similar range of symptoms such as cough; high temperature; chest pain; rapid, shallow breathing; and sputum production.[4, 16] The severity of illness among infected individuals ranges from self-limiting requiring little or no intervention through to diagnoses such as severe acute respiratory syndrome or serious infections of bacterial or fungal origin such as pneumonia or aspergillosis, respectively.[17, 18] Diagnoses of this nature carry a substantial risk of morbidity and mortality as well as extensive healthcare utilisation.[4] Upper RTIs involve the nose, sinuses, pharynx, larynx and large airways. These infections are generally self-limiting in patients without chronic respiratory diseases.[19] Lower RTIs tend to involve more serious presentations and diagnoses such as bronchitis, bronchiolitis and pneumonia and are more likely in patients with chronic respiratory diseases.[16]

In Ireland, COVID-19, influenza and respiratory syncytial virus (RSV) are included in the list of notifiable infectious diseases.[20] Legally there is a requirement for any suspected diagnosis of a notifiable disease or laboratory-confirmed diagnosis of a notifiable disease, such as influenza or SARS-COV-2, to be reported to the Medical Officer of Health, who has responsibility and authority to investigate and control notifiable infectious diseases and outbreaks. In practice this means reporting to the Health Protection and Surveillance Centre which subsequently prepares reports on these notifiable infections. The most commonly reported RTIs in 2022 were COVID-19 with 919,597 cases, influenza with 10,426 cases and RSV with 7,130 cases as well as the bacterial infection *Streptococcus pneumoniae* with 375 infections.[21]

Infections can create the opportunity for a subsequent infection with other pathogens such as SARS-CoV-2, RSV as well as influenza or bacteria causative of pneumonia in what is termed co-infection.[22] This can have severe consequences particularly in individuals with risk factors (for example, those over 65 years of age with co-existing medical conditions).[23-25] Due to the highly transmissible nature of these infections they are also common causative pathogens in outbreaks.[7, 9] Outbreaks are generally defined as two or more linked cases, caused by the same pathogen in the same setting and must be reported in a similar fashion to notifiable diseases.[26]

The strategy for managing these types of infections within the health system involves infection, prevention and control measures such as hand hygiene, isolation if symptomatic and vaccination, as well as treatment should an individual become unwell. Isolating patients that become symptomatic has a particular impact on residential care facilities as individuals that test positive should ideally be placed in a single occupancy room to prevent transmission.[27, 28] Vaccinations are also central to protecting against COVID-19 and influenza. The COVID-19 vaccine is available free of charge in Ireland. Recommendations change over time, although currently everyone aged over 18 years of age is recommended to avail of two initial vaccines as well as two subsequent booster doses.[29] Subsequent booster doses are available for those aged 50 years or older as well as for other groups such as healthcare workers, pregnant people, those with co-existing health conditions, and individuals aged more than five years who are immunocompromised.[30] Vaccination is also available for children aged above four years but requires parental consent. Influenza vaccination for selected individuals may be reimbursed as part of the Health Service Executive (HSE) influenza immunisation programme in Ireland (for example, those aged 65 years or older, healthcare workers or those who are at elevated risk of severe influenza). Individuals that do not fall into these categories can still receive an annual vaccination but must pay for this privately.[31] There is no vaccine currently reimbursed in Ireland that protects against RSV. However, Abrysvo, a vaccine manufactured by Pfizer, received a marketing authorisation in August 2023 from the European Medicines Agency, and is indicated for the passive immunisation of infants from birth to six months of age through administration during pregnancy. The vaccine is also indicated for direct immunisation in adults aged over 60 years.[32] A prophylactic monoclonal antibody therapy, nirsevimab, received its marketing authorisation in October 2022 and is administered as a single dose during or prior to the RSV season.[33] Currently, palivizumab, a monoclonal antibody therapy, can be given on a monthly basis as a preventative measure to infants at risk of a serious RSV infection such as those who are preterm, immunocompromised or have congenital heart disease.[34]

If an individual becomes unwell with COVID-19, influenza or RSV then there are different recommended treatment strategies available. With regards to COVID-19, the HSE has published guidance on its therapeutic management in patients; this includes

hospitalised and non-hospitalised patients.[35] In most individuals COVID-19 is a self-limiting condition and a full recovery is expected within 12 weeks, however in some indivudals symptoms may be long-lasting which can lead to the development of the condition known as Long COVID.[36] Some individuals with COVID-19, however may require additional treatment. Treatment decisions are based on the clinical judgement of the treating clinician and involve respiratory management which is scored using the COVID Respiratory Scale.[35] The strongest evidence available to date for pharmacotherapy involves the prophylaxis of thromboembolism, the use of corticosteroids, and, in rapidly deteriorating patients, the use of tocilizumab.[35] Treatments such as sotrovimab and nirmatrelvir-ritonavir are available in Ireland for individuals with mild to moderate SARS-CoV-2 infection who are at high risk of progression to hospitalisation or death.[37] In relation to influenza treatment, prophylactic treatment with oseltamivir is initiated based on the clinical judgement of the clinician and is recommended for individuals who are at risk of a complicated influenza infection such as those aged 65 years or older, those with chronic respiratory disease or those who are immunosuppressed.[38] RSV can cause bronchiolitis in children aged under two years and babies under six months of age are at increased risk. Bronchiolitis is often treated in hospital. Currently, there are no HSE guidelines published on the management of bronchiolitis in children in Ireland. Similarly, there are no guidelines published by the HSE on the management of RSV in adults. RSV infections in adults can be serious, particularly in those aged 65 years or older, those with underlying heart or respiratory disease, and in immunocompromised individuals.[34]

Given that the different respiratory pathogens present with very similar symptoms, accurate detection of the causative pathogen using clinical judgment alone is challenging. Appropriate treatment for COVID-19, influenza and RSV requires accurate and timely confirmatory diagnosis. The time points at which an infected individual will test positive for a respiratory virus vary. For example, infection with influenza has a narrow window of a few days from the onset of symptoms to the point where viral particles can no longer be detected with an antigen test.[39] Studies examining RT-PCR techniques for the identification of influenza report that viral loads are highest on days two and three.[39, 40] In comparison, infection with SARS-CoV-2 might produce a positive test result a few days after infection and an individual may continue to test positive, using RT-PCR techniques, for several weeks after symptoms have resolved.[41] For this reason, individuals should be tested as close to the onset of illness as possible to inform treatment decisions.

2.3. Burden of disease

In 2020, the Global Burden of Disease Study reported that lower RTIs are the fourth largest cause of disability-adjusted life years (DALY) globally across all age groups.[42]

In children aged ten years and under, and adults aged 75 years and over, the impact of lower RTIs on DALYs is more pronounced.[42] It should be noted that improvements have been made in reducing the global burden of lower RTIs in the past 16 years, especially among young children.[43] This has been driven largely by decreases in several risk factors, though risk factors acknowledged to still be problematic include air pollution, poor nutrition in childhood, and lack of access to appropriate and timely healthcare.[43] As countries transition from a low-middle to high-middle sociodemographic index, the RTI mortality rate in the under five year age group decreases. However, parallel effects are not observed in the RTI mortality rate in older adults.[43] In 2016, there were approximately 120,000 deaths attributable to RTIs in the over 70s in Western Europe.

The COVID-19 pandemic began in late 2019, and to date more than 700 million confirmed cases and nearly seven million deaths have been reported to the World Health Organization (WHO).[44] COVID-19 placed a new and unprecedented strain on resources within health systems across the globe. Recent efforts have been made to assess the burden of disease associated with COVID-19. For example, a 2021 report aimed to assess the life years lost across 81 countries included approximately 1.3 million deaths.[45] Study authors estimated that approximately 20 million life years were lost in total. The average number of years lost per death was 16 years.[45] Furthermore, publications describing the substantial negative consequences COVID-19 had on outcomes such as DALYs, years lived with disability, and years of life lost, have been produced in countries around the world; these include The Netherlands,[46] France,[47] Denmark,[48] Saudi Arabia,[49] Scotland,[50, 51] India,[52-54] Iran,[55] Malta,[56] Mexico,[57] the US,[58] Germany,[59] Italy[60] and Korea.[61] In Ireland, a study estimated that, between March 2020 and February 2021, COVID-19 accounted for approximately 50,000 DALYs, largely driven by premature mortality.[62]

Dealing with RTIs, particularly in the winter months, uses substantial resources and contributes to the phenomenon of winter pressure which has been highlighted in numerous countries.[63-65] An epidemiological study from 2019 compared emergency hospitalisations in the summer (defined as May to August) with winter (defined as November to February) over a three year period in Ireland.[66] The study reported that respiratory conditions such as chronic obstructive pulmonary disease, lower RTIs and pneumonia accounted for 67.8% of emergency respiratory admissions.[66] These admissions were most likely in older adults with additional co-existing medical conditions.[66] There was an increase of 379 emergency respiratory admissions per week in winter, representing a 40.5% increase.[66] The length of stay for respiratory admissions was also reported to increase in winter periods with length of stay increasing from 6.7 days in summer to 7.4 days in winter.[66]

Population aging in Ireland has increased pressure on the acute hospital system as older adults are more likely to have co-existing medical conditions. As such, treatment of these individuals is more complex with longer hospital stays and the requirement for discharge into step-down facilities.[67] This combination of longer hospital stays and delayed discharges results in longer waiting times and hinders appropriate service delivery. In the context of RTIs, there are potential strategies such as at-home intravenous antibiotic therapy, or, possibly, rapid testing and subsequent allocation to appropriate treatment which might lead to reduced lengths of stay and timely discharge.[68, 69] There are limited examples of the use of near-patient testing in Ireland in acute settings; however, the extent to which these impact outcomes such as length of stay or timely discharge it is not clear. For example, a hospital in Limerick assessed the performance characteristics of the Abbott ID now Influenza A&B 2 system. The study reported reductions in healthcare-associated influenza infections during the periods that near-patient testing was available in an emergency department setting, though there was no impact on admissions, intensive care admissions or waiting times for a ward bed.[70]

2.4. Diagnostic testing

Diagnostic methods for respiratory pathogens can test for a singular analyte, defined as a singleplex test, or more than one analyte, defined as a multiplex test. Multiplex tests range in terms of the number of pathogens that they can detect from duplex tests (two pathogens) to highly multiplex tests (five or more pathogens).[71]

Developments in multiplex testing technology mean that samples can be processed outside of the traditional laboratory setting. Samples are processed using specialised devices which are often portable.[72] Using these specialised devices, samples can be analysed by healthcare professionals near to the patient and without transport or communication with a laboratory.[72] This type of testing has become known as near-patient testing. Proposed benefits of near-patient testing include quicker results and subsequent triage to appropriate treatment as well as potential cost savings to the health system.[73]

Multiplex near-patient testing for respiratory pathogens can be broadly separated into two categories: (i) molecular testing; and (ii) lateral flow/antigen testing.[72] Molecular diagnostic methods involve the recognition of specific biomarkers such as nucleoproteins, DNA or ribonucleic acid.[72] Molecular near-patient testing typically requires processing devices which test the sample for selected analytes. These devices range in cost, time to process, accuracy and usability.[74] Examples of molecular testing principles which have been used in near-patient testing include reverse transcription polymerase chain reaction (RT-PCR), recombinase polymerase amplification (RPA) and loop-mediated isothermal amplification (LAMP).[72] With regards to SARS-CoV-2,

influenza and RSV, the gold standard approach to testing involves an RT-PCR-based test on the basis of the accuracy of this method.[72, 75-77] Advantages of RT-PCR based tests are their accuracy in identifying particular viruses. Additionally, RT-PCR techniques can be used to identify strains of pathogens such as influenza A(H1N1) and are a key component of the surveillance infrastructure on emerging viral strains and genotypes. However, as a diagnostic tool RT-PCR has drawbacks such as the length of time to produce a result; this is typically more than two hours for laboratory-based techniques and approximately one hour for near patient testing devices. Seok et al., have highlighted that the ideal NPT diagnostic technology would take approximately 20 minutes to produce a result and would have a sensitivity of approximately 95%.[72]

Antigen tests, often referred to as lateral flow tests, are diagnostic methods which most commonly involve using lateral flow immunoassay (LFA) to detect specific antigens present on particular pathogens.[78] A LFA for respiratory pathogens uses specific antibodies to recognise specific antigen sites on a pathogen and bind to them forming a conjugate.[78] The conjugate can then be detected at a particular point creating a line on the paper indicating a positive result.[78] Some antigen tests use processing devices which interpret and digitally report the results of the immunoassay. Antigen tests have lower sensitivity and specificity than RT-PCR tests.[69] In particular, antigen tests are less accurate and less capable of detecting pathogens when present in lower concentrations, for example, in asymptomatic individuals.[79, 80] However, the advantages of antigen testing include prompt results, typically in under 30 minutes, ease of use, the potential for self-testing, and low cost, as well as the potential for the tests to be mass produced.[69, 72, 75] Furthermore, samples do not always require investment in a processing device as samples can be loaded directly onto the component paper-based device which generates a visible indication of the test result.[72]

Despite the availability of NPTs to diagnose RTIs, (including but not limited to, LFAs), they are currently not in widespread use. For example, a recent point prevalence study conducted in Irish primary care found that NPTs to aid the diagnosis of RTIs were used in fewer than 1% of consultations.[81]

2.5. Multiplex antigen near-patient tests

A review of finddx.org highlighted that there are likely in excess of 80 multiplex antigen-based near-patient respiratory pathogen tests available on the worldwide commercial market. However, this database relies on self-reporting from manufacturers and so the true number of available tests may be higher. It is unclear how many of these would have appropriate regulatory status and be suitable for use in Ireland. Multiplex antigen NPTs must bear a CE mark in order to be placed on the

market in Ireland. This may require assessment by third-party bodies independent from the manufacturer (that is, Notified Bodies) if the test is certified under the In Vitro Medical Devices Regulation (IVDR; in place since May 2022). The IVDR requires that manufacturers demonstrate clinical performance of their products, although the strength and robustness of the clinical performance evidence may vary between products.[82] Manufacturer-reported values for the accuracy of these tests vary, though reported sensitivity and specificity are typically above 90%. Multiplex antigen NPTs also range in terms of their cost and complexity to use (see Table 2.1).

The Haute Autorité de Santé (HAS), the French National Authority for Health, published a report in June 2023, which evaluated multiplex antigen NPTs for the detection of respiratory viruses. The report focused on SARS-CoV-2, influenza and RSV which are the viruses likely to co-circulate during winter months. The tests most frequently examined in the HAS report were paper-based LFAs which are inexpensive, with a typical of cost €1-2 per test, in comparison to RT-PCR NPTs or multiplex antigen NPTs which use processing devices.[15] It should be noted that three multiplex antigen NPTs have been identified which are processed using a benchtop device.[83-86] These tests are substantially more expensive than paper-based LFAs and require purchase of the processing device at a cost of several thousand euro.[85] Potential advantages of these tests are their improved accuracy relative to paper based LFAs, speed relative to RT-PCR NPTs, and ability to be linked with IT systems or patient records.

In 2003, *The WHO Special Programme for Research and Training in Tropical Diseases* published a set of criteria that could be used across all healthcare systems to guide detection and subsequent triage of infectious diseases.[87] The criteria include: 'real time connectivity', 'ease of use', 'affordability', 'sensitivity', 'specificity', 'user friendliness', 'rapid and robust', 'equipment free' and 'deliverable to end users'. These criteria are known by the acronym REASSURED and are the standard used to assess NPTs.[87] A summary of the REASSURED criteria is provided in Table 2.1 together with examples of multiplex antigen NPTs for respiratory viruses. The examples used in this table serve to highlight some to the differences that exist between multiplex antigen NPTs; it is not intended to represent a formal assessment of these devices against the REASSURED criteria.

Table 2.1 Examples of different multiplex antigen NPTs compared against the REASSURED criteria

Criteria used to examine diagnostic testing	Description of criteria	Illustrative examples for multiplex antigen NPTs for respiratory viruses
Real time connectivity	The ability for test results to be interpreted and processed digitally, providing clinicians and decision makers with required clinical information.	Typically samples are loaded onto paper-based LFAs and visually inspected. Examples include the Healgen or MyBio multiplex tests.[88, 89] Manual processing of the result is required. Some tests, such as the LumiraDx SARS-CoV-2 & Flu A/B, Sofia2 Flu + SARS Antigen or BD-Veritor SARS-CoV-2 & Flu A + B, use specialised processing devices which display the result. These processing devices can also be linked with IT systems or patient records. [83, 84, 86]
Ease of specimen collection	Ideally, non-invasive specimens should be collected where possible.	Tests vary in their recommended sample site. For example: Nasopharyngeal swabs are recommended for the Healgen Combo.[88] Anterior Nasal swabs are recommended for the LumiraDx SARS-CoV-2 & Flu A/B.[86] Nasopharyngeal or nasal swabs are recommended for the Sofia2 Flu+SARS Antigen.[83] Nasal swabs are recommended for the BD-Veritor system for the rapid detection of SARS-COV-2 & Flu A+B.[84]
Affordability	Tests should be affordable for the patient or health system.	Tests range in cost. Paper-based LFAs cost approximately €1-2 per test. Some multiplex antigen NPTs require a processing device that may cost several thousand euro.[85, 90] Tests for these devices are typically more expensive than paper-based LFA tests, costing in the region of €10 to €20 per test.[91, 92]
Sensitivity	Tests should avoid false negatives where possible. The WHO recommends rapid antigen tests have a sensitivity of ≥80%.	The test for each pathogen must have appropriate sensitivity; otherwise it hinders the utility of test as a whole in clinical practice. Test sensitivity is discussed in detail in Chapters 4 and 4.4. Manufacturers of multiplex antigen NPTs typically report strong sensitivities well within the WHO minimum requirements. Antigen tests used to identify respiratory pathogens are most sensitive when individuals are symptomatic. This is because symptomatic individuals have higher viral loads which means high concentrations of virus are present in samples.[79, 80]
Specificity	Tests should avoid false positives where possible. The WHO recommends that rapid antigen tests have a specificity of ≥97%.	The specificity of singleplex antigen tests has been noted to be very high, meaning that false positive test results are unlikely.[15]
User friendliness	The procedure for taking and testing a sample should be straightforward, requiring minimal steps and minimal training.	Collecting samples and testing them is relatively straightforward for LFAs with the procedure explained in the user manual. Multiplex antigen NPTs with processing devices require some expertise to use.[85]

Rapid and robust	This refers to patients being able to receive treatment in the same visit as testing. Typically this requires results within 15 minutes to 2 hours. The tests can withstand the supply chain without requiring specialist storage conditions such as refrigeration.	Multiplex antigen NPTs generally take 5-30 minutes for the sample to be taken, tested and the result processed.[78] LFA based tests can be stored at temperatures between 2-30°C, and they may have suitably long shelf lives (one year would be considered optimal).[93] Multiplex antigen tests with processing devices such as the LumiraDx and BD-Veritor test strips must be stored between 2-30°C.[84, 86] The Sofia2, LumiraDx, and BD-Veritor operating temperatures must be between 15-30°C.[83, 84, 86]
Equipment free	The test should not require any specialised equipment. Ideally, any required equipment will be simple and can be solar or battery powered. Equipment should be easily disposed of and recyclable.	Paper-based LFAs are packaged with a swab to take the sample, reagent to prepare the sample, and a testing cassette. No further equipment is required.[88, 89] The LumiraDx, BD-Veritor and the Sofia2 use benchtop processing devices to process tests which can be powered by battery if required.[83, 84, 86]
Deliverable to end users	Tests should be accessible to those that require their use.	Paper-based LFAs are deliverable to end users given their low cost and simplicity to use. Antigen tests with processing devices are more costly and require technical expertise and training to operate.

Key: LFA – Lateral flow assay; NPT – Near patient test; WHO – World Health Organization

2.6. Discussion

This chapter highlights the extensive burden of disease that the three most common identified respiratory pathogens (SARS-CoV-2, influenza and RSV) place on the Irish health system. Furthermore, important factors related to multiplex antigen NPT technology have been highlighted. The majority of individuals infected with SARS-CoV-2, influenza and RSV can recover at home, taking medicines such as paracetamol to manage symptoms. However, patients aged 65 years and older or with co-existing medical conditions are more likely to experience a more serious infection which may require treatment from their GP or, in some cases, hospitalisation. Given these viruses cause similar symptoms it is challenging for clinicians to use clinical judgement alone to identify the causative pathogen.

It is unclear exactly how many different multiplex antigen NPTs have been developed since the COVID-19 pandemic, although it is in excess of 80. The REASSURED criteria, published by the WHO to guide health systems in the detection and treatment of infectious diseases, may be used to assess the characteristics of specific multiplex antigen NPTs.[87] Although the examination of specific tests was beyond the scope of the current report, variation was noted when multiplex antigen NPTs were examined broadly using the REASSURED criteria. There are a number of apparent advantages to these tests. For example, multiplex antigen NPTs are affordable and produce results more quickly than the gold standard RT-PCR, and require no additional equipment. Furthermore, a recent report by HAS highlighted that the specificity of the tests was very high, meaning that antigen tests are likely to produce few false positive results.[15] Singleplex tests for RSV and influenza have been shown to have poor sensitivity.[94-96] Therefore, in the absence of clear evidence, it is possible that multiplex antigen tests may also have poor sensitivity for detecting RSV and influenza. This is discussed further in Chapters 4 and 4.4.

Multiplex antigen NPTs for respiratory viruses are a relatively new technology. New tests are frequently being brought onto the commercial market and are being approved for use by government authorities. For example, the Therapeutic Goods Administration in Australia have approved 16 multiplex antigen tests in 2023 to date. There is substantial variation in the characteristics of these multiplex antigen tests from inexpensive paper-based LFA tests to more expensive tests that use processing devices. For example, LumiraDx SARS-CoV-2 & Flu A/B test and Sofia2 Flu+SARS Antigen or BD Veritor SARS-CoV-2 & Flu A + B both use benchtop processing devices. The manufacturers of these devices report sensitivities and specificities which meet the WHO criteria for antigen tests although these have not yet been validated in clinical practice.[86, 97, 98] These devices, however, are substantially more expensive than paper-based LFA tests.

COVID-19, influenza and respiratory syncytial virus infection are notifiable diseases in Ireland. Therefore, any suspected infection, or laboratory confirmed infection must be reported to the regional Department of Public Health. If multiplex antigen NPTs were used in primary care or residential care facilities then additional administrative processes may have to be implemented to report positive cases which may create an opportunity cost to other areas of practice as well as a financial cost for the administrative task itself. One potential advantage of the tests with benchtop devices is that they can be linked with IT systems to report results.

3. Use of multiplex antigen near-patient tests in Ireland and internationally

Key points

- To date, there are limited examples of, and guidance and or recommendations on, the use of multiplex antigen near-patient tests (NPTs) to detect SARS-CoV-2 and one or both of influenza and respiratory syncytial virus (RSV) in residential and primary care settings.
- One use case in Ireland was identified in the Student Health setting in University College Cork. The multiplex antigen NPT used permitted testing for SARS-CoV-2, adenovirus, influenza A and B and RSV. However, the student population assessed in this study is not representative of the broad population that would attend primary or residential care facilities.
- Two documents providing recommendations were identified. Neither a 2022 joint statement from the Public Health Laboratory Network and Communicable Diseases Network Australia nor the evaluation report from Haute Autorité de Santé (HAS) recommended the use of multiplex antigen NPTs. This was due to a lack of clarity around the medical benefit and performance (in particular, sensitivity) associated with these tests. HAS highlighted the need for further research demonstrating the clinical and public health impact of the tests.
- The World Health Organization (WHO) identified investment in the development and launch of affordable, accessible traditional and new diagnostics platforms (such as multiplex point-of-care respiratory assays) as a priority as part of the Diagnostics pillar of the ACT-Accelerator Transition Plan.
- Multiplex antigen NPTs are still relatively new technologies and so guidance and or recommendations on their use may not have been considered until recently. Although no planned further guidance and or recommendations were identified, it is plausible that more may be published this year to inform winter 2023/2024 plans.

3.1. Background

This chapter provides a synthesis of guidance and or recommendations around the use of, or examples of the use of, multiplex antigen near patient tests (NPTs) in residential and primary care settings in Ireland and internationally.

3.2. Methods

3.2.1. Ireland

The search approaches detailed in Appendix 1 were used to seek relevant guidance or recommendations on how multiplex antigen NPTs are or should be used in residential and primary care settings in Ireland. Searches were conducted on 31 July 2023. The first two hundred results from each search were screened by one reviewer.

Additionally, public health teams in each of the six regional health areas in Ireland, that is Health Service Executive (HSE) Dublin and northeast, HSE Dublin and midlands, HSE Dublin and southeast, HSE midwest, HSE southwest, and HSE west and northwest, were contacted in relation to their knowledge of the use of multiplex antigen NPTs in residential and primary care settings.

One current use case for multiplex antigen NPTs was identified. This was in a Student Health setting in University College Cork (UCC). Members of the Evaluation Team met with representatives from the UCC Student Health and UniCoV-UCC research team (see Section 3.3.1).

3.2.2. International

The search approaches detailed in Appendix 2 were used to seek relevant guidance or recommendations on how multiplex antigen NPTs are or should be used in residential and primary care settings internationally. Documents from the below countries were screened for inclusion in this review. These countries were selected based on a combination of geographical proximity to Ireland, population size, European Union membership and or availability of documents in English:

European Union/European Economic Area

- Austria
- Belgium
- Denmark
- Finland
- France
- Germany

- Italy
- Netherlands
- Norway
- Portugal
- Spain
- Sweden.

Non-European Union

- Australia
- England
- Israel
- New Zealand
- Northern Ireland
- Scotland
- Wales.

Additionally, documents from the following sources were screened: British Medical Journal Best Practice; Canadian Medical Association Infobase; European Centre for Disease Prevention and Control; European Academy of Paediatrics; European Paediatric Association; European Society of Clinical Microbiology and Infectious Diseases; Guidelines International Network; International Network of Agencies for Health Technology Assessment; Institute for Clinical Systems Improvement; and the World Health Organization (WHO). These sources were selected based on their potential to provide relevant recommendations and or their use in the recent Haute Autorité de Santé (HAS) report (searched to identify recent updates since the publication of the HAS report).[15] Searches were conducted from 31 July 2023 to 2 August 2023. The first two hundred results from each search were screened by one reviewer.

3.3. Findings

3.3.1. Ireland

One example of multiplex antigen NPT use in Ireland was identified; this use case occurred in the Student Health setting in University College Cork (UCC), and followed on from UCC's participation in the UniCoV study at UCC. UniCoV is a multi-site, randomised controlled clinical trial led by the National University of Ireland Galway in partnership with Trinity College Dublin, University College Dublin and University College Cork. The aim of the UniCoV study is to explore and compare effective rapid testing and surveillance systems within third-level institutes in Ireland to assist with the early identification of asymptomatic SARS-CoV-2.[99] The development of a surveillance system for third-level institutes would aid in increasing student and staff

confidence and assurance that on-campus is a low risk environment in which to work and study.

The study used a mobile phone application called the UniCoV-Antigen Power App developed by UCC and involved a symptom check, self-administered nasal swab and antigen NPT, with participants also providing a saliva sample which was analysed using reverse transcription polymerase chain reaction (RT-PCR) methods. The four-centre UniCoV study used singleplex NPTs, designed to detect SARS-CoV-2 only. In total, 4,706 participants were recruited to the UniCoV study, and 29,059 UniCov self-test antigen NPTs were completed. The UniCoV study centre in University College Cork recruited 2,296 participants, and recorded 21,213 self-test antigen NPTs. The four-centre UniCoV study ended in June 2022 and results are not yet published.

Building on the experiences of their involvement in the four-centre UniCoV study, the UCC Student Health Department clinicians and the members of the UniCoV-UCC research team explored the use of multiplex antigen NPT from September 2022 through the winter period of 2022/23. Multiplex antigen NPTs were provided by the manufacturer to clinicians. The Healgen multiplex test used is not currently licensed for use for self-testing.[88] Symptomatic patients were asked to self-test for SARS-CoV-2 infection using a standard NPT antigen test. If SARS-CoV-2 was not detected the patient was invited to attend in person at Student Health. Clinicians at UCC Student Health subsequently examined patients, took the patient's history and performed a multiplex antigen NPT which tested for influenza A and B, SARS-CoV-2, adenovirus and respiratory syncytial virus (RSV). Representatives from the Student Health Department in University College Cork highlighted there were fewer than 20 multiplex antigen NPTs performed, and that no participants refused the use of the test. Caution was therefore advised in making any claims on what was achieved in terms of multiplex antigen NPTs in this context beyond identifying potential advantages and disadvantages of the use of multiplex antigen NPTs. Representatives also noted that while other universities involved in the UniCoV study showed interest in using multiplex antigen NPTs for students, there is no record of this taking place to date.

Representatives from UCC Student Health Department noted that an advantage of multiplex antigen NPTs is the relative speed at which an objective diagnosis can be ascertained. This removes the reliance on a clinician-based diagnosis and helps to manage the patient's treatment expectations. Patient confidence in antigen-based NPTs has increased through their use, in particular their use for self-testing during the COVID-19 pandemic. Representatives noted that a positive result for respiratory viruses from a multiplex antigen NPT is likely to be accepted by a patient and may help a clinician in explaining their rationale for not prescribing antibiotics, thereby leading to a reduction in the unnecessary prescription of antibiotics. Patient confidence in antigen NPTs could also result in a higher degree of compliance with isolation

recommendations, with representatives noting that compliance with recommendations was higher when the patient received a positive result for respiratory viruses. When discussing the potential disadvantages of using multiplex antigen NPTs, representatives noted that the test used is currently only licensed for clinician use. They found that the administration of multiplex antigen NPTs extended the patient appointment time by approximately five minutes and while many GP clinics would have practice nurses who could administer the test, the use of these tests is cumbersome and takes time out of the consultation. Furthermore, the multiplex antigen NPT used in this study required the administration of two nasal swabs, and extraction of the sample using a pipette to four separate well cassettes. This introduces greater room for error compared to a singleplex test.

3.3.2. International

Limited information was identified on the use of multiplex antigen NPTs in residential or primary care settings internationally.

In June 2022, the Public Health Laboratory Network and Communicable Diseases Network Australia issued a joint statement on patient referral and requesting of respiratory virus testing for winter 2022.[100] No update was identified for winter 2023. The statement was intended to provide guidance for pathology providers and medical and nurse practitioners who are referring patients with respiratory symptoms for testing following a clinical assessment. It does not relate to self-testing or people self-presenting for testing at respiratory centers and testing hubs. The statement notes that rapid antigen detection can be used as an alternative diagnostic approach for those with COVID-19 symptoms to conserve laboratory testing capacity during times of high prevalence of COVID-19 and where laboratory testing is overwhelmed. However, in relation to multiplex antigen tests specifically, the statement notes that they “are not recommended, given the history of poor performance for the detection of influenza A virus antigen in the past.”

In June 2023, HAS (French National Authority for Health) published an evaluation report on multiplex antigen NPTs for COVID, influenza, and RSV at the request of the Direction générale de la Santé (a department of the French Ministry of Health).[15] This report considered the medical benefit at the individual level (for example, diagnostic performance and clinical usefulness) and population level (for example, reductions in the inappropriate prescription of antibiotics) of using multiplex antigen NPTs “in a city context” (that is, typically during a consultation in a doctor's office). The report focused on the main viruses responsible for acute respiratory infections likely to co-circulate in an epidemic fashion in the winter period (that is, SARS-CoV-2, influenza, and RSV).

HAS searched the websites of 37 national and international organisations and did not identify any recommendations in relation to the use of multiplex antigen NPTs for COVID and influenza or COVID, influenza, and RSV.[15] Initial searches were conducted in December 2022 and sources were monitored for subsequent relevant publications thereafter. Although beyond the scope of the current report, it did identify four recommendations of good professional practice in relation to the use of rapid singleplex antigen tests for influenza, and six in relation to the use of rapid singleplex antigen tests for RSV.

Of the recommendations for influenza, HAS reported that:[15]

- The French Pediatric Society of Pneumology and Allergology recommends the use of rapid antigen tests for influenza if immediate action can be taken on the basis of a positive test result; for example, an early prescription of Tamiflu®.[101]
- The Centers for Disease Control and Prevention and the Infectious Diseases Society of America emphasised the poor sensitivity of rapid antigen tests (in line with the sensitivity requirement of greater than 80% set by the Food and Drug Administration for manufacturers of in vitro diagnostic medical devices).[102, 103]
    - As a result, in 2016 the Centers for Disease Control and Prevention considered that the result of an influenza rapid antigen test should not determine patient treatment.[102]
    - The Infectious Diseases Society of America recommends that these tests should only be carried out in outpatients with influenza-like illness without risk of complications if they are likely to modify the management of these patients.[103] Specifically, they referred to the tests' need to influence the prescription of antiviral treatment, reduce the use of unnecessary antibiotics, or influence the prescription of chemoprophylaxis for high-risk household contacts. However, it does not specify the contexts in which this is likely to occur. They also recommend looking for influenza viruses in outpatients who present with influenza-like illness and are at risk of severe influenza, but without specifying testing methods.
- A recommendation of good professional practice from a consortium of five Spanish societies considered that antigen tests for influenza among pediatric patients should be reserved for situations where rapid molecular tests are not available, although the setting was not specified.[104] It specifies that the test should be done within 24-48 hours following the appearance of symptoms.

Of the six recommendations for RSV identified in the HAS report, HAS reported that they generally indicated that testing for RSV is not helpful, regardless of the testing method (for example, antigen or molecular).[105-110] This is because the diagnosis of bronchiolitis, a chest infection caused by RSV that is the primary reason people (in particular, children) would present with RSV, is clinical, and patient management and treatment does not depend on the causative virus. However, one report recommended that if a clinician wanted to use an antigen test for RSV, they should check with a laboratory for information on newer test technologies, current prevalence of these pathogens, and the generation of algorithms that reduce the risks (due to their poorer diagnostic criteria relative to RT-PCR) of these technologies.[108] In practice, the potential beneficial impact of these tests were considered to be their potential use for epidemiological monitoring of infections and cohorting in the hospital and the avoidance of inappropriate antibiotic prescriptions.[15, 110]

Overall, HAS concluded that there is no evidence of clear medical benefit to using multiplex antigen NPTs.[15] They reported that data on the diagnostic performance of multiplex antigen NPTs are sparse, with manufacturers claiming high levels of sensitivity and specificity but with no studies to date supporting these claims. Additionally, HAS reported that multiplex antigen NPTs may not necessarily protect vulnerable people from exposure to potentially dangerous viruses as they do not test for all potentially harmful viruses and they may generate a lot of false negatives. This means that improved adherence to public health and isolation recommendations among people with a positive test result may be of little benefit if a notable proportion of people with potentially harmful viruses do not have a positive test result. Therefore, clear communication of what the test result indicates and its accuracy would need to be communicated to patients. If patients are symptomatic for a respiratory virus and test negative a recommendation to limit social contact may still be warranted. Testing for RSV in particular may not be useful as it will not inform the diagnosis or treatment of bronchiolitis. Additionally, they noted that the tests could be useful in reducing the inappropriate prescription of antibiotics. This was specifically mentioned in the French context where the scale of this problem is critical, although antibacterial consumption in Ireland is also high and above the European Economic Area average.[111] They may also help in avoiding some consultations or repeat consultations in the emergency department for non-serious infections that could be diagnosed at the first consultation. HAS noted that further evidence from prospective clinical studies demonstrating the clinical and public health impact of these tests is required.

Finally, as part of the World Health Organization ACT-Accelerator Transition Plan (October 2022 to March 2023), support has been given to the development and acceleration of access to affordable COVID-19 rapid antigen diagnostic tests and to the rollout of point-of-care diagnostics at primary healthcare levels and of multiplex multi-pathogen platforms.[112] Although no guidance around the use of multiplex NPTs

was provided, this highlights potential interest in the development of these and related technologies.

3.4. Discussion

Few examples of usage, guidance or recommendations were identified regarding the use of multiplex antigen NPTs to detect SARS-CoV-2 and one or both of influenza and RSV in residential and primary care settings.

In relation to guidance and or recommendations around the use of multiplex antigen NPTs, neither a 2022 joint statement from the Public Health Laboratory Network and Communicable Diseases Network Australia nor the evaluation report from HAS recommended the use of multiplex antigen NPTs; in each case, this was due to a lack of clarity around their medical benefit and performance (in particular, sensitivity).[15, 100] However, there is some interest in the use of these technologies. For example, the need for further evidence from prospective clinical studies demonstrating the clinical and public health impact of these tests was noted by HAS.[15] Additionally, the WHO identified investment in the development and launch of affordable, accessible traditional and new diagnostics platforms (such as multiplex point-of-care respiratory assays) as a priority as part of the Diagnostics pillar of the ACT-Accelerator Transition Plan (October 2022 to March 2023).[112]

No use cases for multiplex antigen NPTs were identified in residential care facilities. One use case in Ireland in a primary care setting was identified in University College Cork. However, the student population assessed in this study is not representative of the broader population that would attend more typical primary care practices. The use of multiplex antigen NPTs in hospital settings in Ireland is being examined in a survey conducted by the Health Protection Surveillance Centre, results for which are due to be published in late 2023.

Discussions with the UCC team highlighted the potential for the tests to reduce inappropriate prescription of antibiotics, which was also highlighted in the HAS evaluation report.[15] Another potential advantage highlighted by the UCC team and in the HAS report was the potential for a positive test to improve patient confidence in their diagnosis, thereby improving their compliance with isolation recommendations. However, patients who present with symptoms but for whom a virus is not detected may still expose vulnerable people to potentially dangerous viruses. To avoid this, tests must be sufficiently sensitive (that is, they must have a low rate of false negatives). However, the HAS evaluation report and a joint statement from the Public Health Laboratory Network and Communicable Diseases Network in Australia raised concerns around test sensitivity for influenza and or RSV.[100]

To conclude, among the identified guidance, multiplex antigen NPT use was not recommended, although it was noted that use of such tests may help in avoiding some consultations or repeat consultations in the emergency department for non-serious infections that could be diagnosed at the first consultation. The need for further

research demonstrating the clinical and public health impact of the tests was identified. Multiplex antigen NPTs are still relatively new technologies and so guidance and or recommendations on their use may not have been considered until recently. Although no planned further guidance and or recommendations were identified, it is plausible that more may be published this year to inform winter 2023/2024 plans.

4. Narrative review of the effectiveness, advantages and disadvantages and feasibility of multiplex antigen near-patient tests in residential and primary care settings

Key points

- A non-systematic literature review was conducted to identify evidence regarding the effectiveness, advantages, disadvantages, and feasibility of using multiplex antigen near-patent tests (NPTs) to detect SARS-CoV-2 and influenza and or respiratory syncytial virus (RSV) in residential and primary care settings.
- The search identified one published study on the effectiveness of a multiplex antigen NPT. Additionally, a June 2023 evaluation report by Haute Autorité de Santé (HAS) included relevant information.
- The one evaluation of the effectiveness of a multiplex antigen NPT identified was a prospective evaluation of a SARS-CoV-2 and influenza multiplex antigen NPT used in a COVID-19 testing centre. The evaluation found that the test had adequate sensitivity and specificity for SARS-CoV-2, however as influenza was not identified during the study period it was not possible to assess the diagnostic performance for influenza.
- HAS reported that there was insufficient data to show the adequate diagnostic performance of multiplex antigen NPTs in a private practice setting (for example, a doctor's office). Studies of singleplex antigen NPTs were reported, which found the tests can have very low sensitivity for influenza and RSV. Additionally, the analysis conducted by HAS of diagnostic information supplied by manufacturers for three multiplex antigen NPTs suggested that these needed to be validated in well-designed research studies.
- HAS noted that multiplex antigen NPTs may have potential benefits for the health system through the potential reduction of some consultations or repeat consultations in the emergency department for non-serious infections that could be diagnosed at the first consultation. However, they did not support other proposed benefits of multiplex antigen NPTs, such as improved adherence to public health recommendations resulting in the protection of vulnerable people from exposure to potentially dangerous viruses.

- Neither the HAS evaluation report nor the current report identified studies investigating the advantages and disadvantages or feasibility of multiplex antigen NPTs in primary and residential care facilities.

4.1. Background

This chapter details the process and findings of a non-systematic literature review to address three research questions (detailed in Section 4.2.1) on the effectiveness, advantages, disadvantages, and feasibility of multiplex antigen near-patient tests (NPTs) to detect SARS-CoV-2 and influenza and or respiratory syncytial virus (RSV) in residential and primary care settings.

4.2. Methods

4.2.1. Research question

This literature review addressed the following research questions:

- What is known about the effectiveness of multiplex antigen NPTs to correctly classify a person as having SARS-CoV-2 and influenza and or RSV or not in residential and primary care settings?
- What are the advantages and disadvantages of using multiplex antigen NPTs for the diagnosis of SARS-CoV-2 and influenza and or RSV in residential and primary care settings (for example, turnaround time, appropriateness of patient treatment, or ability to subtype viruses)?
- What is known about the feasibility (cost and resource implications) of implementing multiplex antigen NPTs for the diagnosis of SARS-CoV-2 and influenza and or RSV in residential and primary care settings?

4.2.2. Study identification and extraction

As the purpose of this chapter is to provide an overview of what is known in relation to the research questions, rather than to provide a comprehensive review of all the literature on a topic, a non-systematic review was performed.

Electronic searches were conducted on 28 July 2023 in Medline via EBSCOhost, Embase via Ovid, and CENTRAL via The Cochrane Library and Clinicaltrials.gov. The search strategy for Medline is presented in Appendix 3. Studies included in the Haute Autorité de Santé (HAS) evaluation report were also reviewed.[15] Retrieved studies were de-duplicated in Endnote and screened for relevance and inclusion in Covidence. Studies were screened by one reviewer.

HTAs, systematic reviews, randomised controlled trials, non-randomised controlled trials, observational studies (but not case reports or case series) and other study

designs (for example, qualitative or mixed-methods studies) that address any of the three research questions were considered eligible for inclusion. The applicability of each document was considered in relation to the Population, intervention, comparator, outcomes, setting (PICOS) framework outlined in Table 4.1.

Data relevant to the three research questions were extracted by one reviewer. Due to the variation in study types, study findings and quality were narratively assessed.

Table 4.1 Population, intervention, comparator, outcomes, setting (PICOS) framework for identification of relevant studies

Population	Adults with a suspected respiratory tract infection.
Intervention	Multiplex antigen NPTs to diagnose SARS-CoV-2 and one or both of influenza and RSV. **Exclusion criteria:** ▪ Self-testing: Tests conducted by patients or self-reported test results.
Comparator	**Any or none:** ▪ Potential comparators could include singleplex tests (that is, tests that detect only one pathogen), self-administered antigen tests, non-antigen tests designed to detect active infection (for example, molecular tests such as RT-PCR tests), or clinical judgement.
Outcomes	Outcomes relating to the performance of multiplex antigen NPTs as well as the potential impact on patient care. Examples include: ▪ test performance o test sensitivity and specificity o turnaround time ▪ cost and resource use ▪ impact on patient care o time to treatment o appropriate treatment with antibiotics/antivirals. **Exclusion criteria:** ▪ Outcomes related specifically to screening or monitoring and or surveillance.
Setting	Residential and primary care settings (for example, general practice, long-term residential care facilities, community mental health facilities, small group homes, etc.).

Key: NPT – near-patient test; RSV – respiratory syncytial virus; RT-PCR - reverse transcription polymerase chain reaction.

4.2.3. Narrative review

Relevant studies identified in the literature search were narratively reviewed.

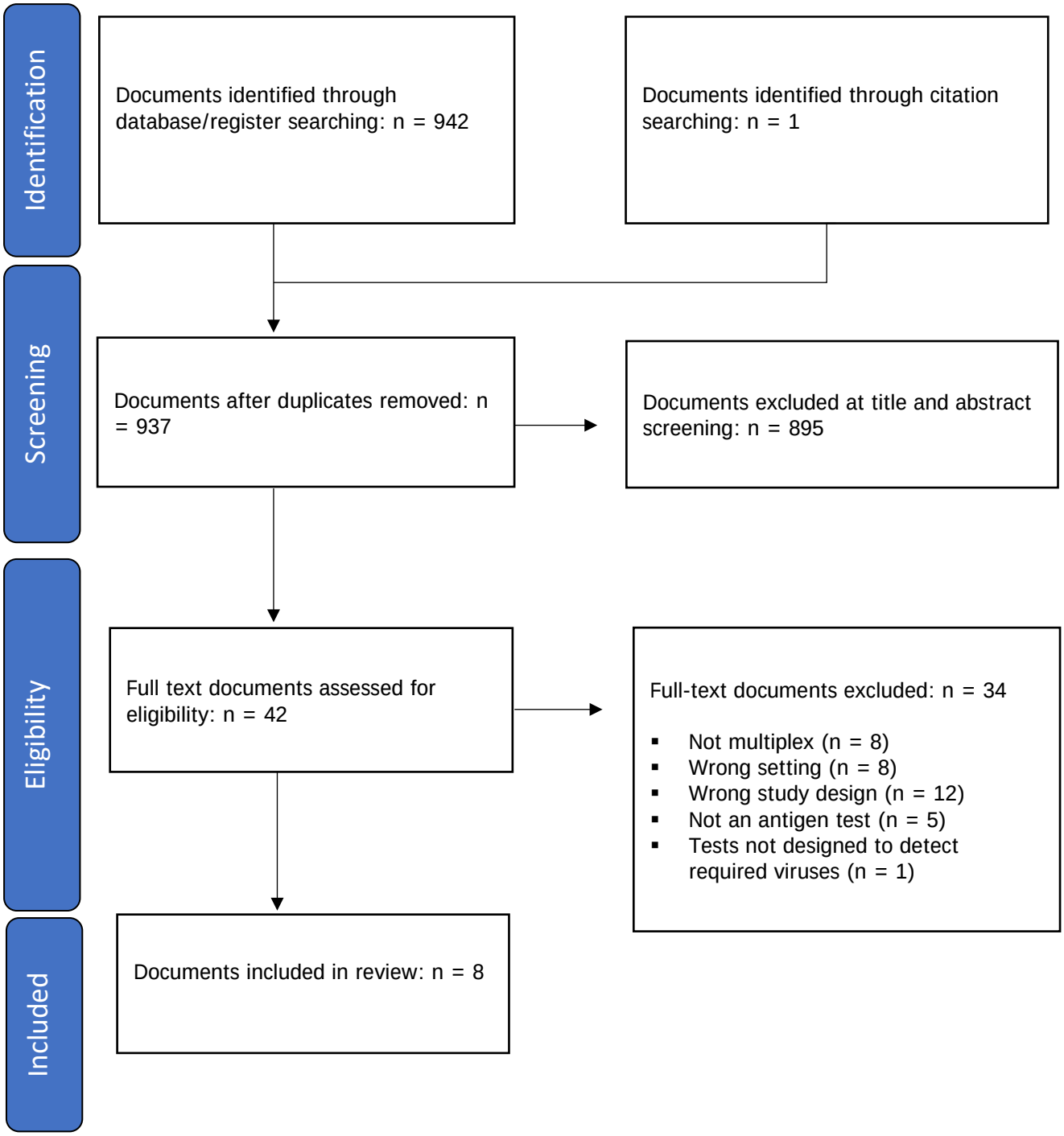
4.3. Findings

4.3.1. Search results

After removal of duplicates, 939 articles remained, of which 895 were excluded based on title and abstract screening. Of the 42 full texts screened for eligibility, 34 were excluded on reading. One prospective evaluation of effectiveness and seven protocols

for trials were included in the narrative synthesis.[113] Figure 4.1 presents a flow diagram of the article screening process.

Figure 4.1. Flow diagram of included studies.



4.3.2. Narrative review

Descriptive characteristics of the included studies are provided in Table 4.2. A narrative review of findings from the HAS evaluation report and studies and protocols identified in the current report are presented below.

In June 2023, HAS (French National Authority for Health) published an evaluation report on multiplex antigen NPTs for COVID, influenza, and RSV at the request of the Direction générale de la Santé (a department of the French Ministry of Health).[15] This report considered the medical benefit at the individual (for example, diagnostic performance and clinical usefulness) and population (for example, reductions in the inappropriate prescription of antibiotics) levels of using multiplex antigen NPTs "in a city context" (that is, typically during a consultation in a doctor's office). The report focused on the main viruses responsible for acute respiratory infections likely to co-circulate in an epidemic fashion in the winter period (that is, SARS-CoV-2, influenza, and RSV). An exhaustive search on Medline and Embase was conducted as part of this evaluation report for the following:

- Studies focusing on the diagnostic performance of duplex antigen tests jointly looking for SARS-CoV-2 and influenza viruses, or SARS-CoV-2 and RSV (January 2019 to February 2023)
- Studies focusing on the diagnostic performance of triplex antigen tests jointly looking for SARS-CoV-2, influenza viruses and RSV (January 2019 to February 2023)
- Systematic reviews and meta-analyses of the diagnostic performance or the clinical utility of antigen tests for influenza viruses (January 2012 to March 2023).

HAS reported that there was insufficient data to show the adequate diagnostic performance of multiplex antigen NPTs, in particular in a private practice setting (for example, a consultation in a doctor's office).[15] They did not identify any studies assessing the diagnostic performance of multiplex antigen NPTs to detect SARS-CoV-2, influenza and RSV. However, they reported that singleplex antigen tests for RSV had very high specificity (≥98%) but modest sensitivity in children (76%) and very poor sensitivity in adults (18%). This indicates that these tests likely generate very few false positive results but many false negative results. In the absence of published studies, HAS requested data from three laboratories that manufacture multiplex antigen tests to detect SARS-CoV-2, influenza and RSV. The reported sensitivity of these tests for RSV (95% to 100%) and influenza (81% to 100%) was substantially higher than the values typically reported in published literature for

singleplex tests that detect these viruses. HAS expressed reservations around the procedures used to obtain the test diagnostic information due to:[15]

- poorly defined target populations (for example, symptomatology and age)
- data obtained from different settings (for example, hospital emergency departments) to their primary focus of general medicine
- non-compliance with certain essential methodological standards (for example, the use of retrospective data)
- very small sample sizes (range: 193 to 334) compared to the size of the theoretical target population.

Regarding the clinical utility of the tests, as reported in section 3.2.2, HAS noted that multiplex antigen NPTs may have a potential benefit for the health system through the potential reduction of some consultations or repeat consultations in the emergency department for non-serious infections that could be diagnosed at the first consultation.[15] HAS also highlighted the findings of two meta-analyses of the effects of influenza antigen tests on the reductions in the inappropriate prescription of antibiotics.

Among children in a hospital setting, one meta-analysis of ten studies found no significant reduction in the prescription of antibiotics following influenza antigen test use integrated with clinical judgment compared to clinical judgment alone (odds ratio=0.64, 95% confidence interval=0.36 to 1.15; p=0.14; I^2=95%).[114] Similarly, among adults and children, primarily in the emergency department, another meta-analysis showed no effect of an influenza antigen test on antibiotic prescription compared to clinical diagnosis when limited to an analysis of seven randomised controlled trials (odds ratio=0.97, 95% confidence interval=0.82 to 1.15; I^2=70%).[115] However, a meta-analysis of the five non-randomised studies included in that review did show a significant reduction in antibiotic prescription (odds ratio=0.64, 95% confidence interval=0.48 to 0.86; I^2=81%). Additionally, they noted that multiplex antigen NPTs are unlikely to be useful in protecting vulnerable people from exposure to potentially dangerous viruses as they do not test for all potentially dangerous viruses and they may generate a lot of false negatives. Further, they noted that testing for RSV may not be useful as it will not inform the diagnosis or treatment of bronchiolitis as diagnosis is based on clinical judgment and treatment is not influenced by the underlying virus.[115]

The current review identified only one study that met the inclusion criteria. This was a prospective evaluation of the accuracy of the QuickNavi-Flu+COVID19 antigen test compared with reverse transcription polymerase chain reaction (RT-PCR) test.[113] Samples taken were also tested using the singleplex QuickNavi-COVID19 and

QuickNavi-Flu2 antigen tests. The study was conducted in a COVID-19 testing centre at Ibaraki Prefecture Japan and included prospectively enrolled individuals suspected of having COVID-19 as well as asymptomatic individuals who were close contacts of confirmed case of COVID-19. Individuals who attended the testing centre were referred from nearby clinics, a local public health centre as well as a hospital. During the study period 2,375 samples were tested with three samples excluded due to a lack of clinical data. There were 1,510 cases of suspected COVID-19 or close contacts to a confirmed case. The included samples were made up of 1,510 nasopharyngeal samples and 862 anterior nasal samples. The sensitivity and specificity of the antigen test for SARS-CoV-2 from nasopharyngeal samples was 80.9% and 99.8%, respectively. The sensitivity and specificity of the test using anterior nasal samples were 67.8% and 100%, respectively. In symptomatic cases, the sensitivities increased to 88.3% with nasopharyngeal samples and 73.7% with anterior nasal samples. No cases of influenza were identified by the QuickNavi-Flu+COVID19 antigen test or the reference real time RT-PCR during the study period. Study authors concluded that the QuickNavi-Flu+COVID19 antigen test showed adequate sensitivity and sufficient specificity for SARS-CoV-2 detection especially in symptomatic patients.

Participants were enrolled from the same population with both groups, those with symptoms of COVID-19 and close contacts of confirmed cases, having samples tested in the same manner. However, demographic data regarding the individuals involved in the study is not provided. The reference RT-PCR test provided an accurate method to confirm participants' infection status and to assess the performance of the QuickNavi-Flu+COVID19 antigen test. No influenza was identified in any samples during the study period. Therefore, it is not possible to comment on the accuracy of the QuickNavi-Flu+COVID19 for identifying influenza. All samples were taken by trained medical professionals using the methods recommended by manufacturers. The study was sponsored by the manufacturers of the QuickNavi-Flu+COVID19 test. The potential impact of confounding factors are not discussed. No information was reported in relation to the cost-effectiveness of the QuickNavi-Flu+COVID19 test.[113]

Of the seven protocols included in the current review, four focused on the examination of the Panbio™ COVID-19/ Flu A&B Rapid Panel and were conducted by the same research team.[116-119] These four studies are being conducted to support the CE conformity assessment procedures. The EU has specifications on certain products which require CE marking. It is the manufacturer's responsibility for declaring conformity with these specifications which involves compiling a technical dossier, and ensuring conformity with all EU–wide requirements.[120] Three protocols focused on the examination of the LumiraDx® SARS-CoV-2 & Flu A/B test.[121-123] Study authors for the seven protocols were contacted regarding the publication of

the trial if it was marked as complete on Clinicaltrials.gov. The trials primarily aimed to assess the diagnostic accuracy of the tests with a secondary aim to assess their usability from the perspective of the clinician and in one case the perspective of the patient self-testing. According to clinicaltrials.gov, two trials have been completed but not yet published results,[117, 122] and it is estimated that two will be completed by January 2024 (see Table 4.2).[116, 118]

Table 4.2 Characteristics of included studies

Study (Country)	Study type	Study status*	Pathogens detectable	Sample size	Setting	Participants	Antigen test	Comparator	Outcomes	Conflict of interest
Estes (US)[121]	Protocol for multicentre performance evaluation	Recruitment not started.	SARS-CoV-2, Influenza A and B	1,500 anticipated	Point-of-care sites	Symptomatic individuals	LumraDx SARS-CoV-2, influenza A&B	RT-PCR	Sensitivity, Specificity, Usability	Sponsored by manufacturer
Farsad (US)[122]	Protocol for multicentre performance evaluation	Study completed, March 2023. Results not yet published.	SARS-CoV-2, Influenza A and B	668	Healthcare clinic, COVID-19 testing centre, research centre	Positive antigen test for SARS-CoV-2, influenza or RSV	LumraDx SARS-CoV-2, influenza A&B. LumiraDx SARS-CoV-2 & RSV	US FDA EUA authorised or 510(k) method	Sensitivity, Specificity, Usability	Sponsored by manufacturer
Kordowich (US)[117]	Protocol for multicentre performance evaluation	Study completed, February 2022. Results not yet published.	SARS-CoV-2, Influenza A and B	2,472	GP centre, hospital clinic	Suspected respiratory viral infection	Panbio™ COVID-19/ Flu A&B	RT-PCR	Sensitivity, Specificity, Usability	Sponsored by manufacturer
Kordowich (US)[119]	Protocol for sample collection evaluation	Recruitment progress not updated since April 2022.	SARS-CoV-2, Influenza A and B	2,000 anticipated	Not clear	Suspected respiratory viral infection	Panbio™ COVID-19/ Flu A&B	RT-PCR	Sample collection	Sponsored by manufacturer
Kordowich (US)[118]	Protocol for multicentre performance evaluation	Recruitment in progress. Estimated completion date of January 2024.	SARS-CoV-2, Influenza A and B	1,531 anticipated	GP centre, hospital clinic	Suspected respiratory viral infection	Panbio™ COVID-19/ Flu A&B	RT-PCR	Sensitivity, Specificity, Usability	Sponsored by manufacturer
Kordowich (US)[116]	Protocol for multicentre, performance evaluation	Recruitment in progress. Estimated completion date of January 2024.	SARS-CoV-2, Influenza A and B	1,531 anticipated	GP centre, hospital clinic	Suspected respiratory viral infection	Panbio™ COVID-19/ Flu A&B	Panbio™ COVID-19/Flu A&B for self-test	Sensitivity, Specificity, Usability	Sponsored by manufacturer

Study (Country)	Study type	Study status*	Pathogens detectable	Sample size	Setting	Participants	Antigen test	Comparator	Outcomes	Conflict of interest
Shinn (US)[123]	Protocol for multicentre performance evaluation	Recruitment suspended as of April 2023.	SARS-CoV-2, Influenza A and B	2,000 anticipated	Point-of-care sites	Suspected COVID-19 and or influenza	LumraDx SARS-CoV-2, influenza A&B. LumiraDx SARS-CoV-2 Ultra	RT-PCR	Sensitivity, Specificity, Usability	Sponsored by manufacturer
Takeuchi (Japan)[113]	Prospective evaluation	Complete and results published.	SARS-CoV-2, Influenza A and B	1,510	COVID-19 testing centre	Suspected COVID-19 or close contacts of confirmed case	QuickNavi-Flu+COVID19	RT-PCR, QuickNavi-Flu2, QuickNavi-COVID19	Sensitivity, Specificity	Sponsored by manufacturer

Key: EUA - Emergency Use Authorization; FDA – Food and Drug Administration; RSV – respiratory syncytial virus; RT-PCR - reverse transcription polymerase chain reaction.
*Study status from clinicaltrials.gov as of 14 September 2023

4.4. Discussion

Limited information on the effectiveness and advantages and disadvantages of multiplex antigen NPTs, and no information on their feasibility, was identified. Regarding the effectiveness of multiplex antigen NPTs, an evaluation report by HAS noted that they likely have very high specificity, meaning that the number of false positive test results is likely to be low. However, concerns were expressed around the sensitivity of multiplex antigen NPTs.[15] Historically, singleplex antigen NPTs have had low sensitivity for influenza and RSV.[94-96] However, some multiplex antigen NPTs report substantially improved sensitivity rates. HAS privately requested and reviewed the data underlying three such tests and they expressed concerns around the procedures used to obtain the test diagnostic information. This was due to issues around the definition of target populations, the settings from which data were obtained, use of retrospective data, and small sample sizes. Indeed, similar issues around lack of a defined target population and use of retrospective data were observed in a 2023 preprint of a manufacturer-funded study in a hospital setting assessing several multiplex antigen NPTs.[124] The one relevant study identified in the current report, conducted in a COVID-19 testing centre, reported sensitivities of 88.3% with nasopharyngeal samples and 73.7% with anterior nasal samples for SARS-CoV-2.[113] However, influenza was not detected in any samples and so diagnostic information could not be calculated. In the absence of well designed, peer-reviewed studies replicating manufacturer reported diagnostic information (discussed in Section 5.4), the sensitivity of multiplex antigen NPTs remains unclear. It is noted that seven protocols for trials examining the Panbio™ COVID-19/ Flu A&B Rapid Panel, LumraDx SARS-CoV-2, influenza A&B and LumiraDx SARS-CoV-2 & RSV tests were identified, and should provide some clarity when the trial results are published.[116-119, 121-123] According to clinicaltrials.gov, two trials have been completed but have not yet published results,[117, 122] and it is estimated that two trials will be completed by January 2024.[116, 118]

Regarding the clinical utility of tests, as reported in Chapter 3, HAS noted that multiplex antigen NPTs may have benefits for the health system through the potential reduction of some consultations or repeat consultations in the emergency department for non-serious infections that could be diagnosed at the first consultation.[15] Additionally, an emergency department-based study in Limerick assessed the performance characteristics of a singleplex influenza antigen NPT, reporting reductions in healthcare-associated influenza infections during the periods that the test was available, although there was no impact on admissions, intensive care admissions or waiting times for a ward bed.[70] However, HAS did not identify evidence to support other proposed benefits of multiplex antigen NPTs, such as improved adherence to public health recommendations resulting in the protection of vulnerable people from exposure to potentially dangerous viruses. Neither the HAS

evaluation report nor the current report identified studies of multiplex antigen NPTs investigating these outcomes in primary and residential care facilities. Therefore, the population impact of multiplex antigen NPTs needs further investigation.

5. Discussion

The emergence of SARS-CoV-2 has resulted in increased pressure on health services to deal with an additional causative pathogen for respiratory tract infections (RTIs). This is in addition to pathogens such as influenza and respiratory syncytial virus (RSV) which have made a longstanding and substantial contribution to winter pressures. The symptoms that these three infections cause are similar and it can be challenging for clinicians to differentiate between the infections using clinical judgement alone. For this reason, diagnostic testing for RTIs has been proposed. Typically, laboratory-based testing methods such as reverse transcription polymerase chain reaction (RT-PCR) are used to identify pathogens. In many cases these tests can detect more than one pathogen, a process known as multiplex testing. RT-PCR based testing methods are highly precise but are likely to take more than two hours to process in a laboratory. It is also costly and requires specialist technicians. Multiplex antigen near-patient tests (NPTs) for respiratory viruses have the potential to identify multiple pathogens and report the result in approximately 15 minutes. They are also relatively inexpensive and require little training. However, the effectiveness and clinical utility of such tests in community and residential care settings remain unclear.

It is unclear exactly how many different multiplex antigen NPTs have been developed since the COVID-19 pandemic, although it is likely in excess of 80. It is unclear how many of these would have appropriate regulatory status and be suitable for use in Ireland. The REASSURED criteria, published by the World Health Organization (WHO) to guide health systems in the detection and treatment of infectious diseases, may be used to assess the characteristics of specific multiplex antigen NPTs.[87] Although the examination of specific tests was beyond the scope of the current report, wide variation was noted when multiplex antigen NPTs were examined broadly using the 'REASSURED' criteria.

5.1. Effectiveness of multiplex antigen near-patient tests

Limited information on the effectiveness of multiplex antigen NPTs was identified. The two guidance documents identified in the current review highlighted the typically low sensitivity of singleplex antigen tests for influenza and RSV.[15, 100] In the absence of evidence demonstrating otherwise, it is possible that multiplex antigen NPTs may also suffer from the same limitation. Indeed, this was found in two studies on multiplex antigen NPTs for the detection of respiratory viruses in settings outside of those examined in the current report. One, conducted in an emergency department, reported sensitivities of 65.9%, 77.8%, and 41.5% for influenza A, influenza B, and RSV, respectively.[125] The second, conducted in a hospital setting, reported a sensitivity of 33.3% for the detection of influenza B.[126]

These sensitivities are all below the 80% that is often used as a minimum cut-off.[15, 127] One study identified in the current report, conducted in a COVID-19 testing centre, reported sensitivities of 88.3% with nasopharyngeal samples and 73.7% with anterior nasal samples for SARS-CoV-2.[113] Although a multiplex antigen NPT was used, influenza was not detected in any samples and so diagnostic information could not be calculated. Test specificities reported in the above studies were high (all 96% or higher), indicating that there can be greater confidence in a positive detection of a viral infection.

In the absence of published data on the effectiveness of multiplex antigen NPTs in primary care settings, a recent evaluation report by the Haute Autorité de Santé (HAS) reported on privately requested data on three multiplex antigen NPTs for which the manufacturers reported high sensitivity rates.[15] HAS expressed reservations around the procedures used to obtain the test diagnostic information due to:

- poorly defined target populations (for example, symptomatology and age)
- data obtained from different settings (for example, hospital emergency departments) to their primary focus on primary care
- non-compliance with certain essential methodological standards (for example, the use of retrospective data)
- very small sample sizes compared to the size of the theoretical target population.

Therefore, it would be beneficial for manufacturer reported diagnostic information to be replicated in well designed, peer-reviewed studies. Further information on the future research required is presented in Section 5.4. The potential implications of low sensitivity rates among tests are discussed in Section 5.2.

5.2. Advantages and disadvantages of multiplex antigen near-patient tests

Proposed advantages of using multiplex antigen NPTs in residential and primary care settings include:

- improved diagnosis and treatment of RTIs
- the potential to avoid inappropriate antibiotic prescription
- increased compliance with public health recommendations (such as isolation), thereby protecting vulnerable people from exposure to respiratory viruses
- avoidance of some consultations or repeat consultations for non-serious infections

It is important to consider the factors that inform treatment of RTIs. For example, there is no single medicine specifically indicated for the treatment of an acute RSV infection. Rather the therapeutic treatment is supportive and focuses on the management of bronchiolitis, a chest infection caused by RSV that is the primary reason people (in particular, children) would present to primary or secondary care settings. Treatment of bronchiolitis is therefore determined by clinical presentation and not by the virus responsible. Detecting RSV may therefore be less likely to impact patient treatment. On the other hand, COVID-19 and influenza have associated treatments and so differentiating between these viruses could inform treatment decisions. Treatments for individuals with influenza who are at a high risk of severe outcomes are recommended early after symptom onset. For example, treatment should be initiated within 48 hours of influenza symptom onset if oseltamivir is being used and within 36 hours if zanamivir is being used. The detection of SARS-CoV-2 may also inform treatment decisions for individuals at a high risk of severe disease outcomes, such as the use of nirmatrelvir-ritonavir, sold under the brand name Paxlovid.

Evidence on the effects of antigen tests in reducing antibiotic prescription is mixed. For example, among children in a hospital setting, a meta-analysis of ten studies found no significant reduction in the prescription of antibiotics following influenza antigen test use integrated with clinical judgment compared to clinical judgment alone (odds ratio=0.64, 95% confidence interval=0.36 to 1.15; p=0.14; I^2=95%).[114] Similarly, among adults and children, primarily in the emergency department, another meta-analysis showed no effect of an influenza antigen test on antibiotic prescription compared to clinical diagnosis when limited to an analysis of seven randomised controlled trials (odds ratio=0.97, 95% confidence interval=0.82 to 1.15; I^2=70%).[115] On the other hand, a meta-analysis of the five non-randomised studies included in that review did show a significant reduction in antibiotic prescription (odds ratio=0.64, 95% confidence interval=0.48 to 0.86; I^2=81%).[115]

Most experts in the HAS evaluation report agreed that multiplex antigen NPTs are of little or no use in reducing unnecessary antibiotic prescription. In their opinion, the decision to prescribe an antibiotic is primarily determined by the clinical picture presented by the patient. Secondly, they believed it is the degree of certainty around the potential presence of a bacterial infection, as opposed to the detection of a virus, that leads to the decision to prescribe antibiotics, especially for children.[15] It was noted that the detection of a virus by a multiplex antigen NPT may help a clinician in explaining their rationale for not prescribing antibiotics. Conversely, in cases where viral infections are not detected by the test but the clinician does not suspect a bacterial infection, it may be more difficult for a clinician to explain their rationale for not prescribing antibiotics, especially if multiplex antigen NPTs have low sensitivity

(that is, they produce many false negative results). Irish General Practitioners (GPs) have reported feeling pressure from patients to prescribe antibiotics, particularly if the patient was paying privately for their services.[128] Prior to the SARS-CoV-2 pandemic, antibiotics were prescribed for respiratory tract infections in 54% of consultations in Irish primary care, above the 32% average for all participating European countries.[81] A point prevalence study of antibiotic prescribing for respiratory tract infections before and during COVID-19 in Ireland identified a reduction in antibiotic prescribing for respiratory tract infections from 54% to 23% in primary care. Therefore, there may be an opportunistic window available while there is a good understanding of viral infections among the general public to further reduce unnecessary antibiotic prescribing.

It is plausible that a positive result in a multiplex antigen NPT may improve patient confidence in their diagnosis, thereby improving their compliance with isolation recommendations and thus protecting vulnerable people from exposure to potentially dangerous respiratory viruses. However, multiplex antigen NPTs do not test for all potentially dangerous respiratory viruses. Further, if multiplex antigen NPTs have inadequate sensitivity, there may be a large number of patients with viral infections that are not detected by the test, and these patients may still expose vulnerable people to respiratory viruses. Therefore, tests with adequate sensitivity are essential.

Despite their potentially poor sensitivity, multiplex antigen NPTs likely demonstrate very high specificity, meaning that a positive detection of a virus is very unlikely to be a false positive. As a result, patients and clinicians may be confident in positive test results. Increased confidence in a diagnosis could lead to greater reassurance of patients and, in particular, parents of sick children, potentially preventing further consultations or attendance in emergency departments. Expert opinion in the HAS evaluation report suggested that this could help relieve some of the overcrowding in emergency departments and surgeries in winter, and avoid unnecessary waiting for patients and or parents of sick children.[15] However, it was highlighted that specific populations in which it would be relevant to test must be defined. It was generally considered that the test would be most relevant to children aged three months or older presenting with high fever which could generate diagnostic doubt.[15]

In addition to the findings of this report there may be further advantages to the use of multiplex antigen NPTs from the perspective of the person tested. These may relate to the value of having a clear diagnosis of a specific infection, which may have personal implications for the individual tested (for example, in informing family members or employers of their infection status). Such advantages were not however referred to in the literature informing this report.

Potential disadvantages of using multiplex antigen NPTs in residential and primary care settings include:

- their inability to identify the strain of virus detected
- time constraints when used in a primary care setting.

All medical practitioners are required to notify the Medical Officer of Health or Director of Public Health of certain diseases, including COVID-19, influenza and RSV. This information is used to investigate cases and prevent the spread of infection, to facilitate the early identification of outbreaks, and to monitor the burden and changing levels of diseases, which can provide the evidence for public health interventions such as immunisation. A limitation of multiplex antigen NPTs is that they do not identify the strain of virus detected. For example, influenza A(H1N1) will be identified by a multiplex antigen NPT as influenza A. Widespread use of antigen-based NPTs could reduce our understanding of dominant or emerging viral strains or genotypes. This is particularly relevant in the context of concerns with respect to emerging SARS-CoV-2 variants of concern, an international pandemic of avian influenza, and the potential introduction of RSV vaccination.

Regarding time constraints when using multiplex antigen NPTs in a primary care setting, the typical turnaround time of a multiplex antigen NPT is longer than the average duration of a GP consultation in Ireland (discussed further in Section 5.3).

5.3. Cost and resource implications

Multiplex antigen NPTs are easy-to-use devices that are typically cheaper than the gold standard RT-PCR. Paper-based lateral flow immunoassay multiplex antigen NPTs typically cost approximately €1 to €2, although some multiplex antigen NPTs require a processing device that may cost several thousand euro.[85, 90] Potential advantages of these tests are their improved accuracy relative to paper based LFAs, speed relative to RT-PCR NPTs, and ability to be linked with IT systems or patient records. Multiplex antigen NPTs typically come in unit form, and do not require specific equipment, laboratory analysis, or specifically trained personnel. Additionally, they can be performed in direct proximity to the patient and produce results quickly, generally in 15 to 30 minutes, although this does not include the time to take the sample and record results. In a 2017 survey on the needs and attitudes of Irish GPs towards near-patient testing, the majority indicated that they would like to have access to point-of-care testing.[129] At the time the survey identified that C-reactive protein testing for bacterial infections was the most sought after point-of-care test, although this may have changed since the SARS-CoV-2 pandemic. The average duration of a GP consultation in Ireland is around 14 minutes, and so the use of multiplex antigen NPTs in a GP setting may create additional pressure in the absence

of additional personnel who can conduct the test.[130, 131] Indeed, experience from the UniCoV study indicated that the use of multiplex NPTs added approximately five minutes to their consultations.[132]

5.4. Future research

Prospective studies conducted in residential and primary care settings that assess the diagnostic performance and clinical utility (for example, changes in antibiotic prescriptions, decreases in emergency department visits or length of hospital stays for RTIs) of multiplex antigen NPTs relative to RT-PCR should be conducted. The UCC Student Health team (that is, the team behind the use case in Ireland detailed in Section 3.3.1) is currently participating in such a study. The 18-month study funded by the Science Foundation Ireland will investigate the use of an optimised version of the mobile application technology developed by UCC and used in the UniCoV project. Seven registered clinical trials primarily aimed at assessing the diagnostic accuracy of multiplex antigen NPTs with a secondary aim to assess their usability from the perspective of the clinician and in one case the perspective of the patient self-testing were identified in the current report, although as the search was not systematic, more may exist.[116-119, 121-123] According to clinicaltrials.gov, two trials have been completed but have not yet published results,[117, 122] and it is estimated that two will be completed by January 2024.[116, 118]

The HAS evaluation report insisted on two conditions prior to the recommendation of multiplex antigen NPTs in a community setting.[15] Firstly, it must be demonstrated that multiplex antigen NPTs have sufficient clinical diagnostic performance in this setting. That is, they must have a sensitivity of greater than or equal to 80% (with a lower 95% confidence interval limit of greater than or equal to 70%) and a specificity of greater than or equal to 99%. HAS noted that:

- these should be demonstrated in a prospective clinical study of people with unknown infection status recruited consecutively or randomly from an outpatient setting
- the population of interest must be clearly defined
- time elapsed since the appearance of the symptoms must be specified
- the samples used for the tests must not have been frozen
- the reference test must be RT-PCR
- the results must be determined blind to the results of the reference test.

Secondly, HAS noted that the population impact of multiplex antigen NPTs must be evaluated. For example, their impact on the rate of antibiotic prescription and on consultations or repeat consultations should be determined. It was suggested that such studies must define which patients (for example, age, clinical picture, or symptom duration) and settings (for example, settings where rapid results are

necessary) these tests would be useful for; such settings could include congregated settings with a large proportion of vulnerable patients, for example, nursing homes, schools, and residential care homes.

Ideally these studies would be conducted independently of parties with potential conflicts of interest, although it may be more feasible for these studies to be conducted by manufacturers in collaboration with health professionals. HAS also noted that, given the incidence of the viruses concerned and the large number of possible investigators (for example, all general practitioners and residential care facilities), such a study should be feasible.

6. Conclusions

Since the COVID-19 pandemic, over 80 multiplex antigen near-patient tests (NPTs) have been developed to detect SARS-CoV-2 and one or both of influenza and or respiratory syncytial virus (RSV). However, evidence on their effectiveness, advantages, disadvantages and feasibility in primary care and residential care facilities is sparse. Further, limited information of their use in Ireland or internationally was identified. The available evidence suggests that the sensitivity of these tests may be low, in particular for influenza and RSV, which could limit their utility. Their utility in primary or residential care settings, such as in reducing inappropriate antibiotic use or emergency department visits, is unclear. Prospective studies conducted in primary care and residential care facilities that assess the diagnostic performance (relative to reverse transcription polymerase chain reaction (RT-PCR) tests) and the clinical utility of multiplex antigen NPTs are required.

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Appendices

Appendix 1 – Search strategy to identify information relevant to the use of multiplex antigen NPTs in Ireland

Organisation	Sites	Search terms
Government	gov.ie	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.ie) 2020..2023
Health Information and Quality Authority	hiqa.ie	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:hiqa.ie) 2020..2023
Health Protection Surveillance Centre	hpsc.ie	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:hpsc.ie) 2020..2023
Health Service Executive	hse.ie	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:hse.ie) 2020..2023

Appendix 2 – Search strategy to identify information relevant to the use of multiplex antigen NPTs internationally

Country	Organisation	Sites	Search terms
International	British Medical Journal Best Practice	bestpractice.bmj.com	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:bestpractice.bmj.com) 2020..2023
	Canadian Medical Association Infobase	joulecma.ca	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:joulecma.ca) 2020..2023
	European Centre for Disease Prevention and Control	ecdc.europa.eu	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:ecdc.europa.eu) 2020..2023
	European Academy of Paediatrics	eapaediatrics.eu	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:eapaediatrics.eu) 2020..2023
	European Paediatric Association	epa-unepsa.eu	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:epa-unepsa.eu) 2020..2023
	European Society of Clinical Microbiology and Infectious Diseases	escmid.org	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:escmid.org) 2020..2023
	Guidelines International Network	g-i-n.net	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:g-i-n.net) 2020..2023
	International Network of Agencies for Health Technology Assessment	inahta.org	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:inahta.org) 2020..2023
	Institute for Clinical Systems Improvement	icsi.org	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:icsi.org) 2020..2023
	World Health Organization	who.int	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:who.int) 2020..2023
Australia	Medical Services Advisory Committee	msac.gov.au	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:msac.gov.au) 2020..2023
	Department of Health	health.gov.au	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:health.gov.au) 2020..2023
	National Health and Medical Research Council	nhmrc.gov.au	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nhmrc.gov.au) 2020..2023
Israel	Government	gov.il	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.il) 2020..2023
New Zealand	Government	govt.nz	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:govt.nz) 2020..2023

Northern Ireland	Government	nidirect.gov.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nidirect.gov.uk) 2020..2023
	Public Health Agency	publichealth.hscni.net	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:publichealth.hscni.net) 2020..2023
UK	Government	gov.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.uk) 2020..2023
	National Health Service	nhs.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nhs.uk) 2020..2023
	National Institute for Health and Care Excellence	nice.org.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nice.org.uk) 2020..2023
	National Institute for Health and Care Research	nihr.ac.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nihr.ac.uk) 2020..2023
	Centre for Reviews and Dissemination	york.ac.uk/crd	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:york.ac.uk/crd) 2020..2023
Scotland	Scottish Medicines Consortium	scottishmedicines.org.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:scottishmedicines.org.uk) 2020..2023
	Healthcare Improvement Scotland	healthcareimprovementscotland.org	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:healthcareimprovementscotland.org) 2020..2023
	Scottish Intercollegiate Guidelines Network	sign.ac.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sign.ac.uk) 2020..2023
Singapore	Government	gov.sg	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.sg) 2020..2023
	National Centre for Infectious Diseases	ncid.sg	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:ncid.sg) 2020..2023
	Agency for Care Effectiveness	ace-hta.gov.sg	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:ace-hta.gov.sg) 2020..2023
Wales	Government	gov.wales	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.wales) 2020..2023
	National Health Service	nhs.wales	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nhs.wales) 2020..2023
Austria	Federal Ministry for Social Affairs, Health, Care and Consumer Protection	sozialministerium.at	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sozialministerium.at) 2020..2023
	Austrian Institute for Health Technology Assessment	aihta.at	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:aihta.at) 2020..2023

Denmark	Danish Health Authority	sst.dk/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sst.dk) 2020..2023
Finland	Ministry of Social Affairs and Health	stm.fi	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:stm.fi) 2020..2023
	Finnish institute for health and welfare	thl.fi/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:thl.fi) 2020..2023
	Finnish Coordinating Center for Health Technology Assessment	oys.fi/fincchta/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:oys.fi/fincchta/en) 2020..2023
France	Government	gouv.fr	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gouv.fr) 2020..2023
	Haute Autorité de Santé	has-sante.fr/jcms	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:has-sante.fr) 2020..2023
Germany	Government	bendesregierung.de/breg-en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:bendesregierung.de) 2020..2023
	Gemeinsamer Bundesausschuss	g-ba.de/english	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:g-ba.de) 2020..2023
Italy	Ministry of Health	salute.gov.it	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:salute.gov.it) 2020..2023
	L'Agenzia nazionale per i servizi sanitari regionali	agenas.it	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:agenas.it) 2020..2023
	Health and Social Services	assr.regione.emilia-romagna.it	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:assr.regione.emilia-romagna.it) 2020..2023
Netherlands	National Institute for Public Health and the Environment	rivm.nl/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:rivm.nl/en) 2020..2023
	Government	government.nl	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:government.nl) 2020..2023
	ZonMw – The Netherlands Organisation for Health Research and Development	zonmw.nl/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:zonmw.nl/en) 2020..2023
Norway	Norwegian Institute of Public Health	fhi.no/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:fhi.no) 2020..2023
Portugal	National Authority of Medicines and Health Products	infarmed.pt	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:infarmed.pt) 2020..2023

Spain	Ministry of Health	sanidad.gob.es/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sanidad.gob.es/en) 2020..2023
	Agencia de Evaluación de Tecnologías Sanitarias	isciii.es	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:isciii.es) 2020..2023
Sweden	Swedish Agency for Health Technology Assessment and Assessment of Social Services	sbu.se/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sbu.se) 2020..2023

Appendix 3 – Search strategy to identify information relevant to the effectiveness of multiplex antigen near-patient tests

Database Name	Medline Complete via Ebscohost

#	Query	Limiters/Expanders
S23	S13 AND S17 AND S22	Limiters - Date of Publication: 20200101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S22	S18 OR S19 OR S20 OR S21	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S21	AB (antigen N3 (test* OR assay* OR immunoassay*)) OR TI (antigen N3(test* OR assay* OR immunoassay*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S20	AB ("lateral flow" N3 (test* OR assay* OR immunoassay*)) OR TI ("lateral flow" N3(test* OR assay* OR immunoassay*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S19	AB ((immunofluorescence OR immunochromatograph*) N3 (test* OR assay* OR immunoassay*)) OR TI ((immunofluorescence OR immunochromatograph*) N3 (test* OR assay* OR immunoassay*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S18	(MH "Immunoassay+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S17	S14 OR S15 OR S16	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S16	AB (Sars-CoV-2 N1 (influenza OR flu OR RSV) N2 (test* OR assay* OR immunoassay*)) OR TI (Sars-CoV-2 N1 (influenza OR flu OR RSV) N2 (test* OR assay* OR immunoassay*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S15	AB ((combo OR combin*) N2 (test* OR kit*)) OR TI ((combo OR combined) N2 (test* OR kit*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S14	TX multiplex*	Expanders - Apply equivalent subjects

		Search modes - Boolean/Phrase
S13	S7 OR S12	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S12	S8 OR S9 OR S10 OR S11	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S11	AB ((new or novel or “19” or “2019” or Wuhan or Hubei or China or Chinese) N3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)) OR TI ((new or novel or “19” or “2019” or Wuhan or Hubei or China or Chinese) N3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S10	AB ((nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or SARS coronavirus 2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2)) OR TI ((nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or SARS coronavirus 2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S9	(MH "SARS-CoV-2")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S8	(MH "COVID-19 Testing+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S6	AB (Respiratory N3 (virus* OR illness* OR infection* OR pathogen*)) OR TI (Respiratory N3 (virus* OR illness* OR infection* OR pathogen*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S5	AB (“Respiratory Syncytial Virus” OR RSV) OR TI (“Respiratory Syncytial Virus” OR RSV)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S4	AB (flu or influenza*) OR TI (flu or influenza*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S3	(MH "Respiratory Syncytial Viruses+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

S2	(MH "Influenza B virus") OR (MH "Influenza A virus+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S1	(MH "Influenza, Human")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

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