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The role of viral diagnostic tests in respiratory tract infections: moving forward

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ABSTRACT

The increased knowledge on virology and the increased potential of their diagnostic has risen several relevant question about the role of an early viral diagnosis and potential early treatment on the management of respiratory tract infections (RTI). In order to further understand the role of viral diagnostic tests in the management of RTI, a panel of experts was convened to discuss about their potential role, beyond what had been agreed in Influenza. The objective of this panel was to define the plausible role of aetiologic viral diagnostic into clinical management; make recommendations on the potential expanded use of such tests in the future and define some gaps in the management of RTI. Molecular Infection Viral Diagnostic (mIVD) tests should be used in all adult patients admitted to Hospital with RTI, and in paediatric patients requiring admission or who would be referred to another hospital for more specialised care. The increased use of mIVD will not only reduce the inappropriate use of antibiotics so reducing the antibiotic microbe resistance, but also will improve the outcome of the patient if an aetiologic viral therapy can be warranted, saving resource requirements and improving patient flows. Implementing IVD testing in RTI has various organizational benefits as well, but expanding its use into clinical settings would need a cost-effectiveness strategy and budget impact assessment.

Keywords: respiratory tract infection, viral diagnostic tests, molecular diagnostic tests

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El papel de las pruebas de diagnóstico virológico en las infecciones de las vías respiratorias: Hay que avanzar

RESUMEN

El aumento del conocimiento virológico y el mayor potencial de su diagnóstico ha planteado una serie de preguntas relevantes sobre el papel de un diagnóstico viral precoz y así la posibilidad de un tratamiento precoz dirigido para el manejo de las infecciones del tracto respiratorio (ITR). Con el fin de comprender mejor el papel de las pruebas diagnósticas virales en el manejo de la ITR, se convocó a un panel de expertos para discutir sobre el posible uso de dicho diagnóstico vírico, más allá de lo establecido en documentos previos acordados para la gripe. El objetivo del panel fue comprender la plausibilidad del diagnóstico viral etiológico precoz en el manejo clínico; formular algunas recomendaciones sobre la posible ampliación del uso de dichas pruebas en el futuro y definir algunas lagunas en la gestión sanitaria de la ITR.

Las pruebas de diagnóstico viral de infección molecular (mIVD) deben utilizarse en todos los pacientes adultos ingresados en el hospital con ITR, y en determinados pacientes pediátricos que requieran ingreso o que sean derivados a otro hospital para recibir atención más especializada. El aumento del uso de mIVD no solo reducirá el uso inadecuado de antibióticos, reduciendo así la resistencia microbiana a los antibióticos, sino que también mejorará el resultado del paciente si se inicia una terapia viral etiológica, reduciendo consumo de recursos y mejorando los flujos de pacientes. Asimismo, existen beneficios organizativos en la implementación de pruebas de diagnóstico in vitro en la ITR que requerirán una estimación del impacto presupuestario y un enfoque de rentabilidad para una mayor penetración en su uso clínico.

Palabras clave: infecciones del tracto respiratorio, pruebas de diagnóstico viral, pruebas de diagnóstico molecular

INTRODUCTION

In February 2023 a consensus on the management of Influenza was published [1]. After the COVID pandemic this helped to raise the awareness on the potential benefits of an accurate management of viral infections [2]. This followed NICE's guideline for the treatment and prevention of neonatal infections, guidelines on the usage of diagnostic tests in emergency care [3] or an evaluation by NIHR on the benefits of early testing and rapid isolation [4]. The increased knowledge on virology and the increased potential of virus diagnostic has risen a series of relevant question on the role of an early diagnostic and potential early treatment on the management of respiratory tract infections (RTI). As with other diseases, the advent of a diagnostic technology paired with targeted therapies has raised questions regarding the pathogenic role of these infections as well as the need to better understand the impact of their use on the management of healthcare burden.

To further understand the role of viral diagnostic tests in the management of RTI, a panel of experts were convened to discuss about their potential role, beyond what had been agreed in Influenza. The objective of this panel was to advise on the plausible role of aetiologic viral diagnostic into clinical management, making some recommendations on the potential expanded use of such tests in the future and to define some gaps in the management of RTI.

METHODS

Six leading Spanish physicians (1 Paediatrician, 1 Infectologist, and 4 Microbiologists from 5 leading Spanish Hospitals) were convened in July 2023 at a round discussion on the definition of the needs and benefits of an aetiologic infection viral diagnostic (IVD) approach and the profiling of the target population of that IVD approach.

The meeting was an unblinded open discussion following a pre-defined semi-structured questionnaire (Supplementary material – Annex 1), facilitated by a third party. Each section of the text corresponds to the discussion around each of the 3 main discussed topics. Despite the meeting was commissioned by a manufacturing company, they did not participate in the meeting, nor directly nor as external listeners.

In terms of evidence grading, the purpose of the meeting was not to construct a Clinical Practice Guideline, but rather a more modest aim of pointing out new avenues to pursue next.

RESULTS

Why do we need aetiologic RTI IVD?. In the current context of upper and lower RTI it is well know that there is a significant number of respiratory syndromes where a coinfection (bacterial and viral) exists. The absence of an accurate viral diagnostic leads to an aetiologic diagnostic for bacterial only, leaving the viral fraction unexplored and unexplained. However, there is increasing evidence on the relevance of viral coinfection in the prognosis of the episodes of RTI [5,6], linking viruses to potential increasing severity of bacterial infections. This includes the detection of SARS-CoV-2 [7] as a relevant prognostic factor [8,9]. Viral infection also constitutes a risk for other clinical events such as acute myocardial infarction, stroke, etc. Several hypotheses have been generated, among them, the downstream dysregulation of the inflammatory cascade could be a prominent factor [10,11]. Therefore, the lack of an accurate diagnostic procedure, where viruses can be precisely diagnosed is not only underperforming care, but could also result in a harm to patients that may be put at risk of unsuspected more severe diseases and/or further complications.

The concept of "*Driver*" versus "*Passenger*" virus needs to be further defined, and the importance and role of each bacterial or viral pathogen on RTI must be clearly elucidated. Understanding whether clinician is facing a bacterial or viral infection is key for future treatment options, and therefore there is a need to clearly identify the viral pathogens in the sample and then to apply clinical judgement to decide whether is it a driver or a passenger virus. In this way, the interaction between the clinician and the microbiologist may shed light into the role of each pathogen in the RTI clinical presentation. The absence of acceptable biomarkers in this field will require the participation of both specialist in the management of the patient and the selection of the appropriate treatment(s). Ruling out the involvement of the '*Big Five*' (namely, Influenza A&B, RSV, SARS-CoV-2, Rhinovirus, and Adenovirus) will certainly be a first step towards an accurate and targeted therapeutic strategy.

An important factor limiting the access and implementation of IVD in RTI is the limited understanding of the potential benefits of that technology. One of the obvious reasons why viral testing is required is the need to incorporate the viral information in the therapeutic decision process, and therefore on the decision for an antibiotic treatment. This has implications for antimicrobial resistance (AMR) policies and important societal consequences of those policies. Within the framework of the PROA project [12], one justification for the existence of specific viral diagnostic tools is the appropriate use of antibiotics.

Beyond this, is important to know if the patient will benefit from an antibiotic or is it just a risk or a potential source of adverse side effects? An appropriately diagnosed patient could benefit, when available, from targeted antiviral therapy, meaning the patient's potential outcome would improve. Limiting the arsenal of treatments to "what we know" is limiting the progress and efficiency of our healthcare systems. Especially now that an increasing number of the "Big Five" have specific viral therapies that could relieve pressure on health services and improve patient outcomes. It might be appropriate to also include parainfluenza virus, metapneumovirus or bocavirus. Furthermore, given that the incidence of SARS-CoV-2 is decreasing as other viruses regain their space, the preponderance of the remaining therapies is worth highlighting.

Taking into account the need to apply targeted viral therapies, there is a need to make an adequate and timely etiological diagnosis. Along with the known benefits of an early start of treatment, taking the necessary measures as soon as possible, combining them with known therapeutic agents is the most appropriate way for an efficient result. This includes the implementation of isolation policies, contact tracing and surveillance when necessary, reducing the need for complementary tests, preventing complications and, no less important, designing bed management policies with the aim of optimizing resources at the hospital level.

However, an adequate analysis of the economic impact of all these benefits has not been carried out yet. Administration, policymakers, and access managers would benefit from such information, as well as a sound economic evaluation.

There are several epidemic aspects that need to be known, as they may affect the management of paediatric and adult/elderly population with a different seasonal post-pandemic pattern than we used to know. After COVID19 pandemic the seasonal pattern of some respiratory pathogens have been lost, or at least have been severely disrupted and not recovered yet. This might have consequences at the level of suspected pathogenic agents when patients presenting with RTI at a certain sesonal time of the year. The knowledge of this changing epidemiology could have an impact on the planning requirements at the level of hospital admissions, emergency care wards and general practitioners (GP).

There is also a need to inform non-specialized medical providers about the relevance of viral etiological diagnosis, in terms of its potential benefits, when and who should perform it, since some of the health providers may not be fully aware of these issues. It is also not adequately known how viral load is not a binary biomarker (present or absent, positive or negative), but rather an important additional viral information that must be co-interpreted with the clinician at different times in the management of the patient, especially if the patient presents an unfavourable evolution

An important question is whether the aetiologic viral diagnostic should be available in both for GP and the Hospital setting, as both can benefit although in different ways. The IVD at the hospital should be available 24hours/7days, and if possible, it should be extended to the home setting. The home setting would be mostly appropriate when the 'deferred treatment onset' is considered, since visits to the clinic facilities could be reduced so decreasing the potential for further spread of infection. This broader access to IVD should be combined with a broader information from the sentinel networks, that should be made more readily available so that prescribing physicians can interpret the results more accurately. The epidemic information provided by surveillance networks and sentinels observatories should be maintained and reinforced after pandemic.

Widespread access to such information raises concerns about the readiness of information systems (and the ability of users to obtain such information), thus being able to timely incorporate and disseminate rapidly changing knowledge. This is necessary throughout the healthcare system, especially in certain clinical facilities, where the result may be available quickly but not accessible to doctors due to administrative constraints. A more "democratic" approach will be necessary for this information network, possibly integrating tools that are not available yet (mobile apps, portable devices, etc).

To achieve that goal and all their benefits be accessible, the tests must be affordable, possibly with a lower price for IVD tests used at the point of care. For many healthcare facilities, the budget impact of widespread use of IVD technologies will be of great concern, especially if the benefits of such early diagnosis are not well explained. Furthermore, an acceptable and methodologically sound economic evaluation of IVD testing in RTI is required for different healthcare settings.

What Tests? Although the group convened around the need of making the tests accessible and almost universal (home, GP and Hospital settings), they acknowledged there is a lack of consensus about which is the appropriate test in every setting.

Hospitals may use molecular IVD (mIVD) testing (based on PCR testing) as it has been shown to be effective and affordable. In adults its use is not discussed. In paediatric patients, although more evidence may be needed and there are budgetary implications, having an IVD test with the same sensitivity and specificity as in adults could lead to its universal use.

In outpatient settings, mDIV would ideally be used as it has been shown to be more reliable (better negative predictive performance). However, given the cost and high number of tests in those primary healthcare facilities, they may not be appropriate in the outpatient setting for all RTI patients, and the expert proposal should be to use non-molecular IVD (nmIVD) testing (ie. antigen-based testing) in outpatient settings. If reduced trial pricing policies could be implemented, then a different access strategy could be pursued. This does not mean that mIVDs should not be available in the outpatient setting, but rather that their use may be limited to some particular cases due to budgetary pressure. Alternatively, nmIVD could be used in epidemic periods, while there is high virus circulation within the community, accepting that its more limited accuracy is balanced by the lower severity of cases. Otherwise, the case would be sent to the hospital where mIVD would be

Table 1 **Suggested tests in healthcare diagnostic settings**

	Hospital Setting		Ambulatory Care	
	Adults	Paediatric	Adults	Paediatric
nmIVD	-	-	++	++
mIVD	+++	+++	+	+

nmIVD: non-molecular infection viral diagnostic
mIVD: molecular infection viral diagnostic

performed (Table 1).

Whatever the test, the result of an mIVD should be available in less than or equal to 30 minutes; Any delay beyond that could potentially lead to dysfunctions in clinical management. In an outpatient setting, especially in paediatrics, test turnaround time (excluding management time) should be less than 10 minutes as there is a risk of overwhelming outpatient settings. Tests based on nmIVD have a lower negative predictive value, the result is influenced by the epidemic predominant virus and should not be administered to any person with less than 48 hours of evolution, although accepting it could have a negative impact on treatment.

CRISPR technologies [13] (gene editing techniques) should be looked at also as a potential future alternative, understanding their potential and the appropriate positioning amongst patients. For any future alternative to be established and acceptable a minimum performance should be required. The minimum would be set at >96% sensitivity and > 98% positive predictive value. This may be challenging, given that regulatory agencies (i.e. ECDC [14]) require only 80% [15]. Stratification of patients' risk should be needed, to reduce the number needed to test.

Any test should cover >50% potential aetiological pathogens to be fully implemented and will only be credible if it has >2 virus targets. This information needs to be contrasted and updated along the epidemiologic information.

For whom? The discussion about to what patients the mIVD should be used can be seen in two different situations: without knowing and knowing the cost. Regarding the former, the group agreed that all RTI patients would be candidates for mIVD, although a stricter criterion would be to use them in outpatient care when a patient is going to be referred to the hospital for further diagnosis or treatment. In this context, clinical judgment must prevail and be the guiding principle; The intensity of symptoms should trigger medical actions, not diagnostic tests. In the hospital setting, regardless of price, all severe RTI patients and those admitted with RTI should have mIVD testing.

In primary care, priority should be given to antigen tests, despite their lower performance capacity, considered too low and unacceptable for many professionals. However, in the hospital setting, at the current cost, all admitted patients should have mIVD testing, especially those on oxygen therapy either in or out of the ICU, the immunocompromised, and those with underlying comorbidities. There was agreement that patients with RTI to be IVD tested should be the same as those considered in the Influenza Consensus document [1]. Similarly, critically ill and immunocompromised patients in the Emergency Unit should have an mIVD test upon arrival.

In the paediatric ambulatory population, there were less consensus on which is the most appropriate attitude. According to the cost, the budget impact may not be affordable, but both at the hospital and the ambulatory setting, an mIVD may be very effective in those children that may be need transferred to a different hospital, or where a targeted therapy may be initiated.

NmIVD and mIVD diagnostic testing should be performed as a priority in those patients in whom knowledge of the precise diagnosis provides additional value and/or targeted therapy can be initiated immediately. Otherwise, it may be perceived as a waste of resources. Patients with RTI without risk factors or serious symptoms should not be tested and non-pharmacological measures should be recommended (masks, social distancing, etc.).

CONCLUSIONS

The meeting highlighted and agreed on the potential use of mIVD in all adult RTI patients admitted to hospital and in some paediatric patients who require admission or who would be referred to another hospital for more specialized care. Increased use of mIVD will not only reduce inappropriate antibiotic use (reducing AMRs), but will also improve patient outcome if targeted viral therapy is initiated, thus reducing resource needs and improving patient flows. Additionally, there are several operational benefits to implementing IVD testing in RTI patients. Many of them will require a budget impact estimate and cost-effectiveness approach before broader implementation.

Because viral treatments must be started early to be as effective as possible, rapid diagnosis (ideally by 30 minutes) at an appropriate cost is needed. NmIVDs are not sufficient for hospitalized patients given their low negative predictive value, but they could be an affordable option in primary care for early management of positive cases.

Effort should be made to better characterize and quantify the benefits of this otherwise well-recognized need to "Treat early to benefit sooner".

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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