Assessment of Vaccines in Europe, the HPV Example: Can the EU Joint Clinical HTA Regulation Result in More Consistent Vaccine Evaluations and Improve Access Across EU Countries?

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INTRODUCTION

Human Papillomavirus (HPV) vaccination is a crucial tool in the prevention of HPV-related diseases and cancers, and it is strongly recommended by healthcare authorities in many countries as part of routine immunisation schedules. However, the reimbursement policies for the HPV vaccine can vary from one European country to another. The specific details of eligibility, reimbursement, and age groups covered can also differ. Bulgaria, Estonia, Greece, and Romania have not yet included boys in their routine HPV vaccination programmes despite HPV infections being responsible for a range of non-cervical diseases in both sexes having serious morbidity and contributing to a substantial healthcare burden. Male HPV vaccination also provides indirect herd protection to girls who have not been vaccinated. In Czech Republic, HPV vaccination is only partially covered by public health insurance. This highlights potential differences in the core procedures for vaccine assessment between those countries and others. Vaccines' market access processes are characterised by the development of recommendations by National Immunisation Technical Advisory Groups (NITAGs) followed by the assessment of health technology assessment (HTA) bodies in less than half of 27 EU member states.

There is a lot of variability in agencies, and therefore processes, involved in vaccine reimbursement assessments and decision-making regarding the inclusion of vaccines in national immunisation programmes (NIPs) or healthcare coverage. This may be a key factor contributing to unequal access to HPV and other vaccines. Additionally, despite that HTA for therapeutic drugs is well established, there is very limited experience in applying HTA methodologies to vaccines, especially for clinical assessments. From January 2025, medicinal products and devices will undergo a joint clinical assessment (JCA) at the European level. Although this won't address the economic factors influencing vaccines' access, all markets will be required to use the JCA as the basis of their decision-making process which can address the potential disparities in assessment of clinical evidence .

OBJECTIVES

This research aims to assess how inconsistencies in vaccine assessments may explain cross-country differences in national HPV vaccination programmes and explore how the proposed methodologies for the EU JCA might address disparities in vaccine access across EU countries.

METHODS

Publicly-available information relating to clinical guidelines for Cervarix (GSK), Gardasil/Silgard, and Gardasil 9 (MSD) in EU27 and the UK was extracted from web searches. Decision-analysis frameworks for NITAGs and HTA bodies and the proposed methods for conducting the JCAs published by the EUnetHTA 21 Consortium were analysed.

RESULTS

All three HPV vaccines were approved by the EMA in 2007 and are indicated for males and females from the age of nine. In many countries, the vaccines have also been reassessed following the introduction of more refined HTA methodologies. We can still observe cross-country variability in the vaccine's recommendations in EU27+UK, illustrated in Figure 1. The majority of countries do not reimburse the full label. The restrictions applied are likely to reflect that the evidence provided for a product was not considered sufficient to prove cost-effectiveness across the full indication, in those markets. It should also be noted that the country's economic situation, healthcare policy and budget will also be criteria that impact on this.

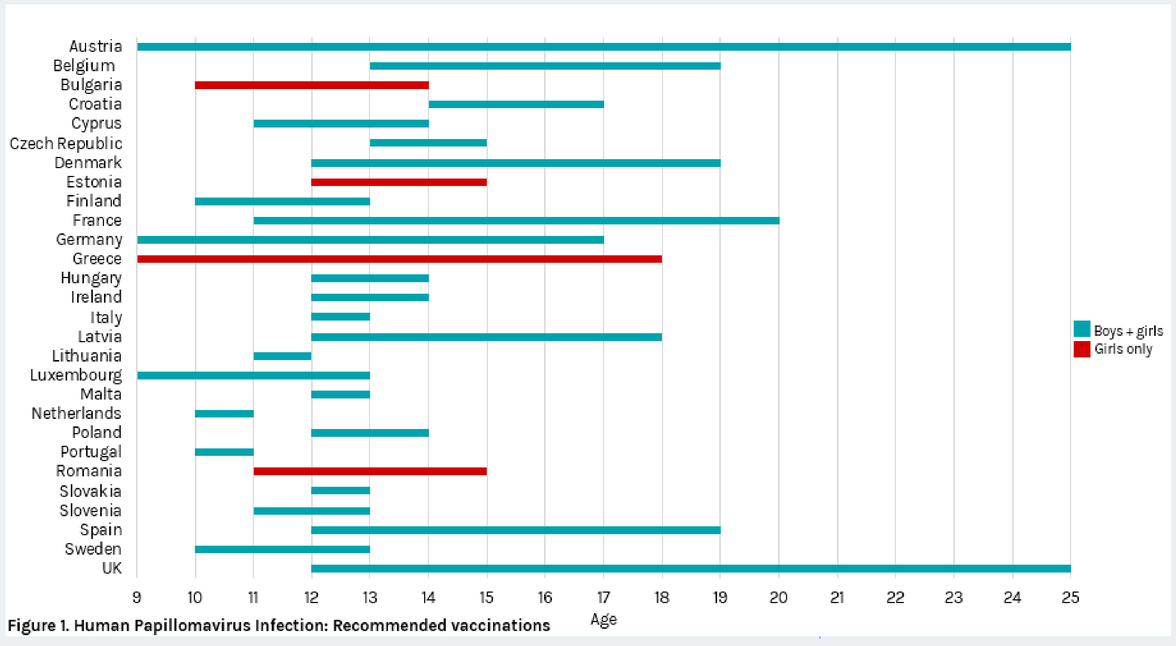

Figure 1. Human Papillomavirus Infection: Recommended vaccinations

	NITAG recommendation	HTA recommendation
Austria	E(BI), Clin.	
Belgium	Clinical, PH	E(BI), E(CE)
Bulgaria	E(BI), Clin.	E(BI)
Croatia	Clin., PH	
Cyprus	E(BI), Clin.	
Czech Republic	E(BI), Clin.	
Denmark	Clin., PH	
Estonia	E(CE), Clin.	E(CE)
Finland	E(CE), Clin.	E(BI), E(CE)
France	E(CE), Clin.	Clin.
Germany	E(CE), Clin.	
Greece	Clin.	E(BI)
Hungary	E(BI), E(CE), Clin.	
Ireland	Clin., PH	E(BI), E(CE)
Italy	Clin., PH	E(BI), E(CE)
Latvia	Unknown	
Lithuania	E(BI), Clin.	
Luxembourg	Clin., PH	
Malta	E(BI), Clin.	E(BI)
Netherlands	E(BI), Clin.	E(BI)
Poland	Local epi.	
Portugal	Clin., PH	
Romania		
Slovakia	Clin., PH	
Slovenia	Clin., PH	E(BI)
Spain	E(BI), E(CE), Clin.	
Sweden	E(CE), Clin.	E(CE)
UK	E(CE), Clin.	

Figure 2. Agencies responsible for vaccines recommendations in EU28 and their main decision drivers
E(BI): Economic, budget impact driver; E(CE): Economic, cost-effectiveness driver; Clin: Clinical driver; PH: Public health driver; Local epi: Local epidemiology

The agency (or agencies) responsible for recommending vaccines' funding and inclusion in NIPs as well as the factors driving these recommendations are presented in Figure 2. Romania is the only country where a NITAG does not recommend inclusion of a vaccine in the NIP and it is also the only country where HPV vaccination is not reimbursed by the national health system. Drivers of NITAG recommendations are mostly clinical and economic factors, and nine countries factor in public health impact. A HTA assessment also takes place in 12 of the 28 countries but most do not have a vaccine-specific decision-analysis framework, meaning vaccines are assessed similarly to therapeutic drugs. However, long-term benefits of vaccinations are not reflected in clinical studies. Evaluations rely mostly on modelling which tend to be complex and subject to a higher degree of uncertainty. The clinical studies evaluating the efficacy of the HPV vaccines followed subjects up to fours years after the first dose of the vaccines whereas it has since been proven protection by the vaccine lasts for at least 10 years. The long-term impact on herd protection and healthcare costs was not assessed.

The EUnetHTA "*Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints*" guideline recommends that outcomes relevant for HTA should be long-term or final where possible. It redefines the controversial use of surrogate endpoints as appropriate when it is not feasible to measure final outcomes, which is particularly relevant for vaccine trials. The basis of a HTA is a set of defined research questions that are to be answered by the assessment and that together define the assessment scope. The EUnetHTA scoping process guideline proposes the inclusion of a PICO survey (Population, Intervention, Comparator, Outcomes) which would allow each member state to provide their national needs with input from clinical experts and patients, ensuring that vaccines' direct and indirect impact on individuals, society and public health are accounted. This would also ensure the scope reflects policy questions from the different healthcare systems. These represent important considerations for national immunisation programmes and to unify the way vaccines are assessed.

CONCLUSION

Complexity, heterogeneity, segmentation, and limited transparency of processes may explain the discrepancies in vaccines' access observed between countries. The development of a joint clinical "fit for purpose" HTA would ensure HTA takes place for vaccines across European countries and may help gain greater consensus on vaccines assessment. While the organisation of immunisation programmes remains a national competence, consistency in processes forming part of vaccine assessment and decision-making pathways has the potential to lead to more predictable, rapid, and transparent evaluations which may lead to greater consistency in how vaccines are reimbursed and more importantly included in NIPs

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