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Commentary

Quadrivalent influenza vaccines in low and middle income countries: Cost-effectiveness, affordability and availability

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ABSTRACT

In high-income countries, there is an increased tendency to replace inactivated seasonal trivalent influenza (TIV) vaccines with quadrivalent (QIV) vaccines as these are considered to give a greater public health benefit. In addition, several recent studies from the USA and Europe indicate that replacement with QIV might also be cost-effective; however, the situation in low- and middle-income countries (LMIC) is less clear as few studies have investigated this aspect.

The paper by de Boer et al. (2008) describes a dynamic modelling study commissioned by WHO that suggests that in LMICs, under certain conditions, QIV might also be more cost-effective than TIV. In this commentary, we discuss some important aspects that policymakers in LMICs might wish to take into account when considering replacing TIV by QIV.

Indeed, from the data presented in the paper by de Boer et al. it can be inferred that replacing QIV for TIV would mean a 25–29% budget increase for seasonal influenza vaccination in South Africa and Vietnam, resulting in an incremental influenza-related health impact reduction of only 7–8% when a 10% symptomatic attack rate is assumed. We argue that national health budget considerations in LMIC might lead decision-makers to choose other investments with higher health impact for a budget equivalent to roughly a quarter of the yearly TIV immunization costs.

In addition to an increased annual cost that would be associated with a decision to replace TIV with QIV, there would be an increased pressure on manufacturers to produce QIV in time for the influenza season requiring manufacturers to produce some components of the seasonal vaccine at risk prior to the WHO recommendations for influenza vaccines.

Unless the current uncertainties, impracticalities and increased costs associated with QIVs are resolved, TIVs are likely to remain the more attractive option for many LMICs. Each country should establish its context-specific process for decision-making based on national data on disease burden and costs in order to determine whether the health gains out-weigh the additional cost of moving to QIV. For example, immunizing more people in the population, especially those in higher risk groups, with TIV might not only provide better value for money but also deliver better health outcomes in LMICs.

Countries with local influenza vaccine manufacturing capacity should include in their seasonal influenza vaccine procurement process an analysis of the pros- and cons- of TIV versus QIV, to ensure both feasibility and sustainability of local manufacturing.

1. Introduction

Since 2010, WHO has recommended that Member States develop evidence-based policies for seasonal influenza vaccination for different risk groups [2]. In many low- and middle-income countries (LMICs) there is as yet no such policy although this is

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beginning to change and uptake is in latest years increasing in various countries, in particular in the Latin America region [3].

Policy makers and programme managers in LMICs do face a number of questions and choices when considering the introduction of seasonal influenza vaccines or replacement of existing vaccines with newer products in their national immunization programmes (NIPs).

Different approaches to improve traditional trivalent inactivated seasonal vaccines (TIVs), have been licensed recently including a high dose (60ug) TIV for adults older than 65 years [4], and an oil-in-water emulsion adjuvant, MF59, containing vaccine, that gives significantly higher titres of homologous and heterologous (cross-reactive) haemagglutination inhibition (HI) antibodies and better protection against laboratory-confirmed influenza [5]. Approaches focusing on alternative administration routes have also been licensed and include intranasal (needle-free) administration for a live attenuated influenza vaccine (LAIV) [2]. The quadrivalent vaccine (QIV) approach, which consists of a vaccine with four instead of three vaccine viruses: (A/H1N1, A/H3N2, B/Victoria and B/Yamagata), was developed in part to resolve a potential B virus mismatch of TIVs [6] and has been available since 2011. Increasingly, this latter approach (QIV) is being chosen in high-income markets such as the USA and Europe, raising the question of their value to LMICs. In WHO's 2012 position paper on influenza vaccines [2], no preference for one approach over the other (TIV or QIV) is expressed.

WHO has provided guidance on how economic evidence should be used for vaccine introduction decisions [7], but a recent systematic review on cost-effectiveness of influenza vaccines in LMICs concluded that compared to the situation in high-income countries, there is limited evidence on cost-effectiveness of influenza vaccines and methods applied vary in quality [8]. Related to the latter: heterogeneity of methods used for costs of influenza burden in LMICs calls for standardizing research, data collection and evaluation methods for both direct and indirect cost components [9–11]. While low-income countries generally prioritize interventions on their affordability, middle and high-income countries increasingly include cost-effectiveness analysis while setting priorities in decision making on introducing vaccines or replacing existing vaccines for improved versions in NIPs.

In many seasonal influenza immunization programmes in LMICs, the most common approach is the use of TIVs produced in eggs. Replacing such a vaccine with a QIV version means an additional cost and potential safety aspects (see hereunder in Section 4) to the programme against as yet little known benefits. The current QIV price is substantially higher than the TIV price. A recent systematic literature review on the health economic consequences of QIV, identified 7 studies in 5 high income countries with published vaccine prices; the incremental vaccine price (in 2015 US $) of QIV over TIV was found to range between US $2 and US $5 [12]. In the US market, QIV is rapidly replacing TIV and only one manufacturer still also offers TIV for a 20% lower price: QIV Afluria from Seqirus has a 2017 public market dose price for adults of $11.95 against $9.50 for TIV Afluria [13].

To gain more insight in this matter, WHO commissioned a modelling study requesting under which scenario's replacement of TIV with QIV might be cost-effective in LMICs. The results of this study are now reported in the paper bij the Boer et al. for 2 LMICs (South Africa and Vietnam) and Australia [1]. An earlier article describes the comparative health outcomes of TIV and QIV for South Africa and Australia [14].

In this commentary, we put the results of the study by de Boer et al. into perspective, focusing on budget impact and other criteria rather than cost-effectiveness thresholds alone. We further point to several additional important characteristics of QIVs to take into account when considering replacing TIV for QIV in seasonal influenza vaccination programmes in LMICs in particular when it comes to safety, feasibility and availability.

2. Replacing TIV for QIV: Is it worthwhile to spend significant additional budget to achieve a relatively modest health impact?

The study on cost-effectiveness by de Boer et al. [1] used individual-based simulation models capturing influenza spread described by Milne et al. [14]. These were used to determine vaccine effectiveness and cost-effectiveness of QIV versus TIV over an 11-year period (2003–2011) in the Agincourt community in South Africa, the Thai Nguyen community in Vietnam and the Albany community in Australia. The number of vaccine doses used each year was set at 15% of the population and prioritized to vulnerable sub-groups: first to HIV-infected individuals, then to elderly aged 65+ years, and the remaining to children aged <5 years.

De Boer et al. conclude that in all three countries influenza vaccination per se led to a considerable reduction of influenza morbidity, hospitalizations and deaths. They further suggest, referring to a previously estimated willingness to pay (WTP) threshold for LMICs of I$1,045/QALY, that QIV would only be cost-effective in Vietnam when a seasonal attack rate (SAR) of 10% is assumed (I$640/QALY). If for Vietnam an official threshold of Thailand (I$8,400/QALY) would be used, QIV would be the most cost-effective alternative at SAR's of 5% and 10%. In South Africa, QIV would not be cost-effective. For Australia, an earlier used WTP threshold of I $32,900/QALY would imply that TIV would be the most cost-effective alternative at a SAR of 5%, but QIV at a SAR of 10%.

To interpret these results for national decision making it is useful to look at impact effects at population level. Table 1 (extracted from the data provided by de Boer et al. [1]) summarizes the budget and health impact results assuming a 10% SAR and 15% of the population immunized in the two study sites in South Africa and Vietnam. Replacing QIV for TIV including administration costs would mean a significant budget increase for influenza vaccination of 29%, 25% and 15% in South Africa, Vietnam and Australia respectively, resulting in a relatively modest health impact of respectively 7.9%, 7.5% and 1.6%.

Perhaps the most relevant question for national programme managers, who generally work within a fixed budget, is what would the additional health gain be if the additional budget required for QIV (e.g. an additional I$17 million for South Africa, see Table 1) is spent on purchasing additional TIV instead? Using the individual based simulation model by Milne et al. [14], it can be inferred that such use of an additional number of TIV doses in all three countries results in numbers of cases averted that are very close to or higher than what is achieved through QIV (Fig. 1). For Australia an increase number of TIV doses gives even better value of money compared to QIV in terms of cases averted for all vaccination strategies because of fewer mismatches of TIV over the 11-year period.

A recent publication by Jamotte et al. about potential benefits of QIV in Latin America may serve to illustrate the dilemma faced by national decision makers [15]. This industry-supported paper analyses the public health impact and economic benefits of QIV over TIV in Brazil, Colombia and Panama. Using a static model, they conclude that "using QIV instead of TIV in Brazil between 2010 and 2014 would have prevented 365,000 influenza cases over 5 years with associated cost offsets equivalent to US$13 million" or US $2.7 million annually. If we assume that QIV vaccine procurement costs are US $2 more than a TIV vaccine (using the lowest published incremental vaccine price of QIV over TIV as reported in [12] and look at the data provided in Table 1 of ref. [15], then the total yearly additional cost of QIV vs TIV in Brazil would reach

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