**Concept note: Phase II work on modelling next-generation influenza vaccines**

**Objective:**

Explore and quantify the expected global health and economic impact of next-generation influenza vaccines (NGIVs) with different characteristics

**Background:**

NGIVs have the potential to revolutionise the vaccine market. Current seasonal influenza vaccines are re-formulated each year to accommodate genetic changes in circulating strains. However, they have limited uptake in low- and middle-income countries (LMICs) due to resource limitations and in some settings, lack of a distinct influenza season.

The desired product characteristics for NGIVs broadly fall into two categories: (i) transformative vaccines, where protection is expected to last 10 or more years, and (ii) incremental vaccines, where protection lasts 2-3 years, and vaccine efficacy is higher than current seasonal vaccines. Vaccines of both types are currently under development at varying stages of development, and there is considerable uncertainty both in which vaccine type will be first-to-market, and how efficacious it will be.

Development of NGIVs will require sustained investment from international donors and manufacturers. Potential donors require evidence of return on their investment in terms of net global public health benefit, while manufacturers require evidence of a return on investment in terms of net revenues from vaccine sales. For both stakeholders, it is critical to determine how a vaccine with different characteristics could be used in order to achieve the greatest public health impact and value for money. Early estimation of these characteristics will also allow global procurement agencies such as Gavi, the Vaccine Alliance, to plan the medium-to-long term investment possibilities.

For donors, global public health benefit will be driven by the burden in LMICs [6]. Uptake of current influenza vaccines has been poor in these settings, so next-generation vaccines offer the potential for considerable market expansion, albeit at the cost of peri-annual rather than annual sales. However, sales in these markets will need to overcome obstacles such as lack of awareness of disease burden, multiple competing public health priorities, and lack of technical capacity to estimate vaccine impact. Such markets can also only be sustained by differential pricing, which will require healthy sales in high-income countries (HICs) to make cross-subsidisation possible.

In HICs, influenza vaccine programs have been shaped by model-based evaluations of the health and economic impact of vaccination [7–10]. However, there has been less exploration of the role of seasonal vaccination in middle-income countries (MIC) [11,12] and even less in low-income countries (LIC), possibly because influenza vaccines are not seen as a high priority in resource limited settings, but also because of limitations in data and technical capacity for both building and using models for decision making. This is beginning to change, with for example National Immunization Technical Advisory Groups (NITAGs) in Kenya and Thailand discussing seasonal influenza vaccination, with the latter basing their discussions using a cost-effectiveness evaluation [12].

**Work being done in Phase I (December 2021 – December 2022)**

Phase I of this work was funded by the US Centres for Disease Control and Prevention (CDC) and Wellcome Trust, via Ready2Respond. In this phase, we adapted existing models of seasonal influenza fitted to epidemiological data in Kenya, Thailand and the United Kingdom. We extended these models to multiple seasons by adapting the well-established fluEvidenceSynthesis modelling framework [13]. We then estimated the health impact and cost-effectiveness of NGIVs with different profiles in these three settings, under different assumptions about natural immunity.

**Aims and Objectives of Phase II (January 2023 – December 2023)**

Phase I was important proof of principle and an early indication that NGIVs could have tremendous impact and be cost-effective, but for greatest applicability the analysis needs to be extended to other countries. Phase II of the project will extend the models in three countries to the rest of the world. As well as being a valuable contribution for global decision-makers in its own right, the global modelling work will be a key input into work towards a Full Value of Influenza Vaccines Assessment (FVIVA) proposed by the World Health Organization (WHO) in order to determine the market size and return on investment of these vaccines to developers, countries and global donors.

***Task 1: Fit simplified models to countries with influenza activity and strain data***

We will leverage the best fitting parameter distributions from epidemiological and economic models of NGIVs in Kenya, Thailand and the UK to extend this work to countries with sparser data. Here we will include around 10 countries where both burden and subtype information are publicly available, based on the WHO Global Influenza Programme and published burden studies. This includes a range of countries across geographic regions.

**Task 2: Extrapolate dynamic model to regions without data using statistical models.**

We will use statistical methods to extrapolate vaccine impact from countries with fitted models to other settings. These include the countries we fitted to in the first phase, additional countries fitted to in Task 1 and countries that other groups have already fitted the fluEvidenceSynthesis model to (primarily countries in Europe). We will classify countries or regions based on techniques such as cluster and conjoint analysis, based on factors such as: i) demography (of country and cases), ii) contact patterns [29], iii) seasonal patterns, iv) strains, v) geographic region.

*Deliverable A: Completed fitted models to countries with data, and extrapolated models to other countries.*

**Task 3. Assess health and economic value and market size of NGIVs for seasonal influenza.**

We will estimate the incremental health impact and economic value of NGIVs in every country (compared to current seasonal influenza vaccines). We aim to address how potential vaccine characteristics (e.g. high efficacy, expected duration of protection, etc) affect the impact and cost-effectiveness of these vaccines.

*Deliverable B: Paper or report on the health and economic impact and market size of incremental and transformative NGIVs.*

**References**

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