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Development of World Health Organization (WHO) recommendations for appropriate clinical trial endpoints for next-generation Human Papillomavirus (HPV) vaccines

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ABSTRACT

The World Health Organization (WHO) serves as a key organization to bring together experts along the continuum of vaccine development and regulatory approval, among its other functions. Using the revision of WHO's guidelines on prophylactic human papillomavirus (HPV) vaccine as an example, we describe the process by which (1) a need to revise the guidelines was identified; (2) a group of stakeholders with complementary expertise and key questions were identified; (3) a scientific review was conducted; (4) consensus on revisions was achieved; (5) guidelines were updated, reviewed widely, and approved. This multi-year process resulted in the consensus that regulatory agencies could consider additional endpoints, such as persistent HPV infection or immune equivalence, depending on the design of the HPV vaccine trials. Updating the guidelines will now accelerate vaccine development, reduce costs of clinical trials, and lead to faster regulatory approval.

1. Introduction

The process to recommend a commercial vaccine has multiple steps and safeguards taken to generate international consensus among multiple stakeholders. This process ensures that recommendations are based on the quality of scientific data and are made with the health of the public in mind. Using the World Health Organization's (WHO) recent revision of its recommendations and standards for prophylactic human papillomavirus (HPV) vaccines, "Guidelines to assure the quality, safety and efficacy of recombinant human papillomavirus virus-like particle vaccines" (Technical Report Series 962, Annex 1), as an example, we describe the multi-year, multi-step process that was undertaken to arrive at the updated guidance [1].

WHO's global written standards, the Technical Report Series (TRS), serve many functions: (1) to provide guidance for national regulatory agencies and manufacturers to assure vaccine quality, safety, and efficacy; (2) to serve as the basis for national legislation; and (3) to represent WHO vaccine prequalification, thereby legitimizing vaccine procurement by United Nations agencies.

In 2006, the WHO established the technical guidelines to assure the quality, safety, and efficacy for prophylactic HPV L1-virus-like particle (VLP) vaccines (TRS 962, Annex 1) [1]. These recommendations were developed in the context of the safety and efficacy of the recently available prophylactic vaccines at that time, the bivalent (Cervarix, GlaxoSmithKline) and quadrivalent (Gardasil, Merck) recombinant VLP HPV vaccines [1]. Both of these first-generation HPV vaccines target HPV types 16 and 18, which are associated with 70% of the global cervical cancer burden, and the quadrivalent vaccine also targets non-oncogenic HPV types 6 and 11 [2]. Primary data demonstrated very strong efficacy for both vaccines against the disease endpoints for licensure: high-grade pre-invasive lesions of the cervix, vulva, and vagina [3,4].

In 2009, the WHO published a position paper on prophylactic HPV vaccines, recommending the routine use of these vaccines in national immunization programs [5], and both vaccines were pre-qualified by the WHO that same year. These two steps enabled international global health partnerships to procure and distribute the HPV vaccine. In subsequent years, advances in HPV vaccine research compelled the WHO to consider revising its guidance on vaccine efficacy evaluation – specifically, whether or not to consider alternate clinical endpoints for next-generation vaccine trials.

In this paper, we summarize the process implemented by the WHO to (1) identify a need for guideline revision; (2) assemble stakeholders to establish relevant questions; (3) critically review the current

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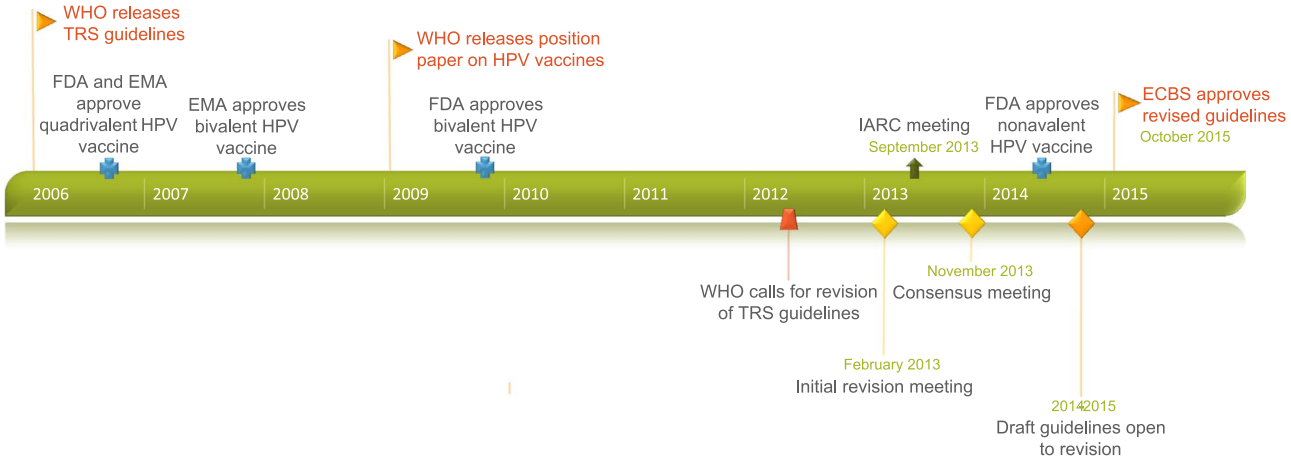

FDA: Food and Drug Administration (USA)
EMA: European Medicines Agency (EU)
WHO: World Health Organization
IARC: International Agency for Research on Cancer
ECBS: European Committee for Biological Standardization
TRS: Technical Review Series
HPV: human papillomavirus

Fig. 1. A timeline of HPV vaccine adoption and corresponding WHO guidelines, with a focus on guideline revision.

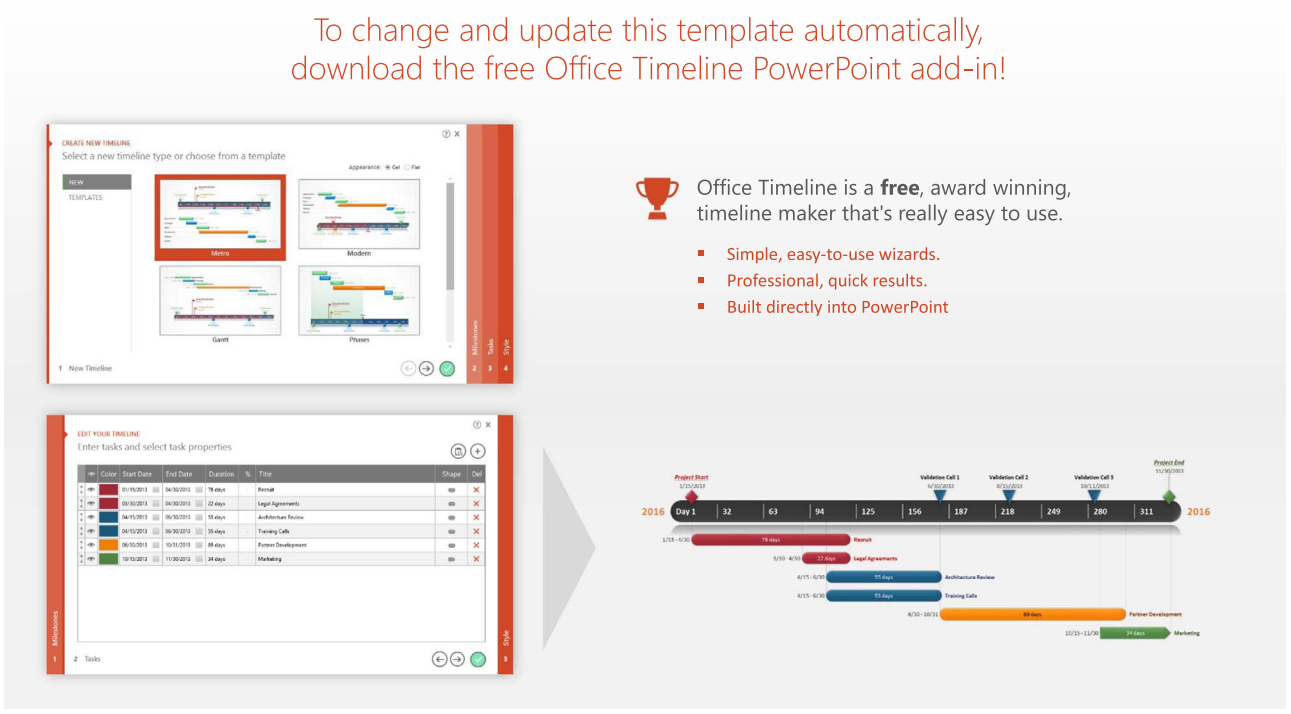

Fig. 1. (*continued*)

evidence on HPV epidemiology; (4) establish consensus on appropriate clinical endpoints for regulatory evaluation of next-generation HPV vaccines; and (5) update guidelines. Fig. 1 presents a timeline of this process. These key steps were necessary for the approval of the new guidance, named "Recommendations to assure the quality, safety, and efficacy of recombinant human papillomavirus virus-like particle vaccines" in October 2015 [6].

2. Identifying a need for guideline revision

Pivotal trials for the current L1-VLP vaccines against HPV types 16 and 18 were powered for efficacy against a disease endpoint, CIN2+. This outcome was chosen due to the unethical and impractical nature of waiting for development of cervical cancer. Given high vaccine efficacy among vaccine-type naïve patients, these vaccines reduce the incidence of preinvasive lesions significantly [4].

With proven efficacy of current vaccines, increasing understanding of HPV epidemiology, and ongoing innovation of next-generation HPV vaccines, the WHO initiated a process to evaluate additional trial endpoints for new prophylactic HPV vaccine trials in 2012. The WHO recognized the need for next-generation HPV vaccines. New vaccines could allow for several innovations: increased coverage of non-16/18 oncogenic disease, new production and delivery platforms, potential use in younger age ranges, simpler administration schedules and