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Opportunities and challenges in delivering influenza vaccine by microneedle patch

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ABSTRACT

Introduction: Simple and efficacious delivery methods for influenza vaccines are needed to improve health outcomes and manage possible pandemics both in the United States and globally. One approach to meeting these needs is the microneedle patch (MNP), a small array of micron-scale needles that is applied to the skin like a bandage.
Methods: To inform additional technical developments and the eventual introduction of MNPs for influenza vaccination, we interviewed key opinion leaders in the United States for insights into the opportunities and challenges associated with this technology, particularly its potential for self-administration.
Results: All interviewees expressed high support for administration of influenza vaccine in MNPs by health care providers and for self-administration in groups supervised by a provider. Self-administration via prescription and over-the-counter purchase of MNPs received lower levels of support. Interviewees also highlighted priorities that should be considered in the ongoing development of an influenza vaccine MNP, such as confirming efficacy and ensuring safety for self-administration. For patient and health care provider acceptability, important attributes are ease of use, short wear times, and an easily accessible application site.
Discussion and conclusions: Stakeholders agreed that using MNPs can help increase coverage, facilitate easy and safe delivery, reduce the cost of vaccination, and decrease the global morbidity and mortality associated with influenza. Another opportunity for this delivery method is the potential for self-administration. The prospect of reduced provider training requirements, increased thermostability, and high patient and provider acceptability makes it an attractive option for use in remote and low-resource settings worldwide. However, in addition to the technological challenges associated with producing the patch, developers must be mindful of cost considerations and key product attributes or requirements, such as usability, wear time, and proper disposal, that can affect how the product will be received in the marketplace.

1. Introduction

Worldwide, influenza causes approximately five million cases of serious illness and 250,000–500,000 deaths each year [1]. If a highly virulent pandemic strain were to emerge in today's interconnected world, it would have the potential to kill more than 60 million people, with a disproportionate number of deaths occurring in low-income countries [2].

In the United States, annual estimates of influenza-associated deaths between 1976 and 2007 ranged from more than 3000 to 49,000, depending on the characteristics of the circulating virus strains [3]. Despite recommendations that all persons 6 months of age and older be vaccinated annually, only 31% of healthy adults aged 18–49 years, 57% of healthy children aged 6 months to 17 years, and 66% of adults aged 65 and older received a seasonal influenza vaccine during the 2012–2013 season [4]. While many factors influence the decision to be vaccinated, simple and efficacious delivery methods for influenza vaccines could improve vaccination rates and health outcomes, and could help manage possible pandemics in the United States and globally, especially because the influenza vaccine must be administered every year.

An alternative delivery method is using microneedles, which are less than one millimeter long and allow administration of

Abbreviations: KOLs, key opinion leaders; MNP, microneedle patch; OTC, over-the-counter.

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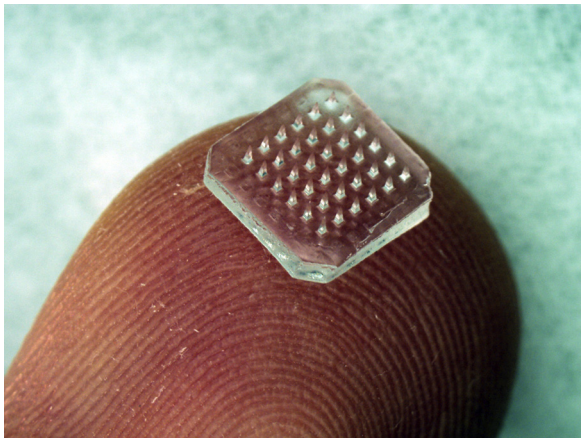

Fig. 1. A dissolvable microneedle patch currently in development. Photo credit: Georgia Institute of Technology.

vaccines or drugs into the epidermis and dermis of the skin (Fig. 1), rather than intramuscularly, the typical route. Intradermal delivery of influenza vaccine by microneedles can lead to longer-lasting and more-robust antibody responses than intramuscular vaccination in mice, suggesting the possibility of improved efficacy [5–17]. Clinical studies comparing intramuscular delivery of influenza vaccine to intradermal delivery in liquid form through hollow minineedles and microneedles have shown a superior immune response in the elderly when an equal dose is administered intradermally, and equivalent immune responses in younger adults with administration of a reduced dose [18–24].

With the emergence of microfabrication manufacturing technology over the past several decades, microneedles have been developed by academic laboratories and pharmaceutical companies [25]. There are four basic types of microneedles: (1) solid microneedles used for skin pretreatment rather than direct drug delivery, (2) solid drug-coated microneedles, (3) polymer microneedles that contain the drug and release it when they dissolve, and (4) hollow microneedles for liquid delivery into the skin [26].

When microneedles are fabricated in arrays on a backing that can be applied to the skin like a bandage, the device is called a microneedle patch (MNP) [25]. Unlike hollow microneedles, which deliver liquid vaccine, MNPs require vaccine reformulation into a solid format and offer the potential for improved vaccine thermostability (which could reduce or eliminate the requirement for storage in the cold chain), reduced packaging volume, and decreased sharps waste. Solid-coated MNPs and dissolvable-polymer MNPs are being developed for delivery of influenza vaccine [27]. Although further research is needed to determine whether solid MNP delivery of influenza vaccine will allow for the use of reduced antigen doses or improve the efficacy of vaccine in humans, there are also other potential advantages of MNP delivery of influenza vaccine, for example improved patient acceptability and the possibility of self-administration, which would allow for health care provider-supervised group vaccination or unsupervised patient self-administration as a prescribed or over-the-counter (OTC) product.

The history of commercialization efforts for other new influenza vaccines provides important lessons for the introduction and market potential of new vaccination methods. In recent years, intranasally delivered, live attenuated influenza vaccine, FluMist®, and a prefilled, hollow microneedle delivery system, Fluzone Intradermal®, have become available [28]. Each has significant advantages over intramuscular delivery of influenza vaccine, including increased acceptability [29–31], and in the case of FluMist®, superior efficacy and cost-effectiveness [32–34]. However, neither vaccine is licensed for all age groups, and both are priced higher than other influenza vaccines, factors which have likely decreased their adoption rate. [32,35,36]. Research on both FluMist® and Fluzone Intradermal® indicated that self-administration would be feasible, but neither is currently licensed for this [37–39].

In order to inform additional technical developments and the eventual introduction of MNPs for influenza vaccination, we interviewed key opinion leaders (KOLs) in the United States for insights into the opportunities and challenges associated with this technology, particularly its potential for self-administration.

2. Materials and methods

We invited 69 KOLs nationwide with expertise in different areas of influenza vaccination to participate in interviews about influenza vaccine delivery by MNP. Many were current or past representatives of liaison organizations for the United States Public Health Service's Advisory Committee on Immunization Practices or were current or former members of that committee.

Questionnaires about the perceived benefits of MNP influenza vaccination in different delivery situations were developed, sent to external experts for review, and finalized in an iterative process. Each participating KOL received two questionnaires in advance of a telephone interview. The first was a uniform set of nine questions for all interviewees, and the second was a set of questions tailored to the interviewee's area of expertise. In addition to the questionnaires, each interviewee received an information sheet on MNPs for influenza vaccination and potential scenarios of use. Researchers used the questionnaires to conduct a structured telephone interview lasting 30–60 min with each interviewee.

The interview questions required both quantitative and qualitative answers and highlighted the following areas: priority policy issues; impact on coverage rates; acceptability to health care providers and patients; and the importance of various product attributes, including wear time, dissolvable versus coated MNP technology, and thermostability. Interviewees also were asked to list the top three issues that should be considered in the introduction of a vaccine delivery technology with the long-term goal of self-administration. These answers were analyzed for the terms or phrases used most frequently, which are listed as major findings in the presentation of results.

The PATH Research Determination Committee ruled that this activity was not a human subjects research study, and, therefore, no ethics committee review was conducted. Interviewees were informed that their names would not be used in any report or dissemination of results.

3. Results

Twenty-five KOLs agreed to be interviewed (response rate of 36%), including 10 policymakers, seven health care providers, three waste management employees, two state immunization program representatives, two regulatory experts, and one purchasing specialist.

3.1. Support for different delivery scenarios

Results of the quantitative questions asking interviewees to indicate the level of support their organizations would likely express for use of the MNP for influenza vaccination in each of four scenarios are presented in Fig. 2. Not all interviewees answered all questions; the number responding to each question is given in figure legends.

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