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# Summary of knowledge gaps related to quality and efficacy of current influenza vaccines

Michael Pfleiderer[a,b], Jean-Hugues Trouvin[c], Daniel Brasseur[a,d,e], Marta Gränstrom[a,f,g], Ragini Shivji[h], Manuela Mura[h,*], Marco Cavaleri[h]

[a] Vaccine Working Party of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)
[b] Federal Institute for Vaccines and Biomedicines, Paul-Ehrlich-Straße 51-59, 63225 Langen, Germany
[c] Paris Descartes University, School of Pharmacy, Health Safety and Public Health Department, Paris, France
[d] Agence Fédérale des Médicaments et des Produits de Santé, Batiment EUROSTATION, bloc 2, place Victor Horta, 40/40, B-1060 Brussels, Belgium
[e] Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)
[f] MTC, Karolinska Institutet, Stockholm, Sweden
[g] Paediatric Committee of the European Medicines Agency (EMA)
[h] European Medicines Agency (EMA), 7 Westferry Circus, Canary Wharf, London E14 4HB, United Kingdom

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ABSTRACT

Influenza viruses are a public health threat, as they are pathogenic, highly transmissible and prone to genetic changes. For decades vaccination strategies have been based on trivalent inactivated vaccines, which are regulated by specific guidelines. The progress in scientific knowledge and the lessons learned from the A(H1N1)2009 pandemic have highlighted further the need to improve current guidelines, including the immunogenicity criteria set by the CHMP in 1997, and to promote the discussion on the shortcomings encountered, e.g. the evaluation of vaccine efficacy in the paediatric and elderly populations, the measurement of the naivety of a population, the impact of prior immunity on subsequent vaccinations, and the technical issues with the serological assays for detection of immunity and immunogenicity.

The authors attempted to summarise and tackle key gaps in the existing evidence concerning quality and efficacy of influenza vaccines, aiming at favouring a common understanding and a coordinated approach across stakeholders.



## 1. Introduction

Influenza represents a serious public health threat and vaccination provides the most effective countermeasure. Competent authorities have set guidelines and requirements to regulate and harmonise quality, safety and efficacy of influenza vaccines for authorisation [1], which following the experience with the A(H1N1)2009 pandemic [3] and the advance in scientific knowledge need updating. Key gaps in the existing evidence concerning quality and efficacy of influenza vaccines and proposals on how these gaps could be addressed, who should be involved and with which level of priority are summarised here, in order to favour a common understanding and a coordinated approach across stakeholders.

## 2. Immunogenicity and serological assays

One of the biggest challenges in influenza vaccination is the evaluation of vaccine efficacy mostly by means of correlates of protection that were established decades ago. It is now generally recognised that there is an urgent need to redefine marker(s) or relevant level(s) of immunity that would represent better correlates of protection for influenza in different clinical (paediatric, adult, elderly) and epidemiological (seasonal, prepandemic, pandemic)

*Abbreviations:* CMI, cellular mediated immunity; CoP, correlate of protection; ELISA, enzyme-linked immunosorbent assay; HA, haemagglutinin; HI, haemagglutination inhibition assay; HPAIV, highly pathogenic avian influenza viruses; HPLC, high-performance liquid chromatography; LAIV, live attenuated influenza vaccine; LC–MS/MS, liquid chromatography–tandem mass spectrometry; M2, matrix protein 2; NA, neuraminidase; NP, nucleoprotein; RCTs, randomised clinical trials; RT-PCR, reverse transcription-polymerase chain reaction; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; SPR, surface plasmon resonance; SRH, serial radial haemolysis; SRID, single radial immunodiffusion assay; TIV, trivalent inactivated influenza vaccines; VN, virus neutralisation assay.

* Corresponding author.
*E-mail address:* manuela.mura@ema.europa.eu (M. Mura).

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**Table 1**
Tabulated summary of gaps, actions and stakeholders involvement.

| Identified gap | Proposed action | Proposed priority (1–4)[a] | Proposed involvement |
|---|---|---|---|
| | **Multidisciplinary issues** | | |
| 1. Target product profile of inactivated influenza vaccines<br>(a) The target product profile for (seasonal and pandemic) currently available influenza vaccines which is applicable to different populations/epidemiological situations is not sufficiently defined. | To be demonstrated by preclinical and clinical studies and quality development/characterisation studies | 1 | 1 (a), (b) and (d) Co-operative effort (Industry, IMI)<br><br>1 (c) Industry |
| (b) Whether HA remains the antigen of choice and whether the required vaccine antigen content is and should be the same for different types of vaccines (split, subunit or whole virion), even amongst different manufacturers, is uncertain. | It needs to be established whether it is relevant to apply the same fixed quantity of HA/other antigen per vaccine dose. | 3 | |
| (c) The current content of NA per dose of each vaccine type (and its inter-batch consistency) is unknown. | If NA is important to the immunogenic profile, then its role (and eventually its titre) in the target product profile should be established.<br>Consideration should be given to characterise the neuraminidase (NA) antigen as far as technically feasible in the vaccines currently in use or under evaluation for CoP (see 7). | 1 | |
| (d) There is at this stage insufficient information to establish optimal antigen/adjuvant ratios for the different types of influenza vaccine to establish the systematic need for adjuvant in different formulations for use in various scenarios/populations. | To be demonstrated by preclinical and clinical studies and quality development/characterisation studies | 3 | |
| | **Area of quality** | | |
| 2. Potency assays for inactivated influenza vaccines<br>(a) There is significant inter- and intra-lab variability for the SRID assay. | The current knowledge on the quality characterisation of influenza antigens (HA, NA, or any other influenza antigen)/formulations should be improved and the significance of these quality aspects on vaccine immunogenicity, efficacy (CoP) and safety needs to be understood and controlled as necessitated. | 1 | Co-operative effort (Industry, EDQM, OMCLs). See clinical section for responsibility for studies on correlates of protection. |
| (b) There is not an exact correlate between vaccine potency (as determined currently by SRID) and clinical outcome. The SRD titre will depend on the production and formulation system and also the reagents used on an annual basis, independent of adjuvant use. It is therefore unclear whether the immunogenic potential is the same for different vaccine types (e.g. whole vs. split vs. subunit vaccine), different formulations, and differing manufacturing processes. | | 1 | |
| (c) Alternate state of the art assays to determine potency, especially those methods providing a biologically relevant potency measure (functionally active protein) and which can be also stability-indicating are not yet available. Considering the poor reliability and robustness of SRID as a potency/dose assay, there is a need to establish correlation between alternative assay results and clinical outcome. | Alternative assays (e.g. optimised SRID, HPLC, ELISA, SDS-PAGE, LC–MS/MS, SPR) should be developed and their use should be validated with the clinical outcome. | 1 | |
| 3. Production systems for inactivated influenza vaccines<br>(a) The nature of traditional technologies to manufacture and characterise these vaccines means that it is inevitably more difficult to characterise all components accurately and precisely define vaccine composition. Companies should collate and expand their product specific knowledge using different strains. | Efforts should be made to gain an enhanced product and process knowledge based on historical production experience and state-of the-art process and product characterisation studies. Investigating the behaviour of different strains in a specific vaccine/production system would allow better and quicker adaptation of the production system to a novel pandemic strain. | 2 | Industry to propose additional investigations on various strains to increase knowledge database for their systems. |