EMA guidelines on influenza vaccines

High level hearing on the implementation of the Council Recommendation on seasonal influenza vaccination

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Influenza vaccines centrally authorised

Use of the vaccine

- Seasonal vaccines
- Pandemic preparedness vaccines (authorised in the interpandemic period)
- Pandemic vaccines, authorised during a pandemic (from the above - or via emergency procedure)
- Zoonotic influenza vaccines

Type of vaccine construct

- Inactivated non-adjuvanted (split, subunit and whole virion)
- Inactivated adjuvanted (split, subunit)
- Live attenuated
New Guideline for influenza vaccines

• Public consultation closed (July 2014 - end of January 2015)
• Currently under revision based on comments received
• Approx date of publication of the final document: end of 2015
• Entry into force: TBC – approx 6 months after publication

• Changes to improve clarity: covering all flu vaccines and all epidemiological scenarios in one document; modular structure: 1) Quality; 2) Non-clinical and Clinical; 3) Regulatory/procedural

• Changes to improve evaluation of future vaccines: revised requirements based on current knowledge and past experience (lessons learned 2009, scientific advice)

• Scope: LAIV, inactivated (un)adjuvanted split subunit, whole virion. Broadly applicable to: alternative antigens (e.g. not full HA), recombinant surface antigens, DNA- or VLP-based vaccines expressing surface antigens.
Major changes to improve evaluation of seasonal influenza vaccines

• **Correlates of protections:** need to better define existing CoPs

• **Clinical Efficacy required in infants 6-36 months** (naïve population) in principle for all seasonal vaccines (due to limited data)

• **Annual strain change for seasonal:** small confirmatory clinical trials no longer required based on decades of experience

• **Continuous monitoring** of vaccines’ effect via vaccines effectiveness studies and enhanced safety surveillance plans to be conducted yearly.
Major changes to improve evaluation of seasonal influenza vaccines

Correlates of protections (inactivated HA vaccines)

So far:
- HI titre 1:40 represented a reasonable CoP for efficacy of 50-70% against influenza
- Since 1970s, evidence indicates need to better define CoPs, may vary according to e.g. specific age group or vaccine type

New recommendations:
- Efforts in development encouraged to support identification of CoPs
- Immunity against HA: HI/SRH and VN; HI titre 1:40 no longer sufficient for approval, distribution of titres across population and % of vaccinees above specified cut off levels; GMTs, SC, pre/post-vacc comparisons;
- Broader investigation of immune responses by measure of anti-NA and CMI, especially in elderly
Seasonal influenza vaccines

MAA - Requirements for authorisation - Efficacy

- **Non-adjuvanted**: Non-inferior immunogenicity vs. a comparable authorised vaccine in adults, elderly and children >3y. In children 6-36m efficacy trial required.

- **Adjuvanted**: advantage needs demonstration (i.e. by superior immunogenicity vs. non-adjuvanted authorised comparable vaccine in adults, elderly and children >3y. Children 6-36m efficacy trial.

- **Special groups**: careful consideration for e.g. patients with comorbidities and immunocompromised

- **Live attenuated**: efficacy required in any group included in the indication.

- **Novel vaccines** (e.g. whole virion, recombinant): no comparable vaccines authorised → demonstration of clinical efficacy required in principle
Seasonal influenza vaccines

MAA- Requirements for authorisation - Safety

**All vaccines type**

- Total size of safety population should consist of at least 3000 individuals (rare ADRs – 1 in 1000): children or adults or elderly (based on indication - stratified);
- Specified age groups in addition to any of the above (e.g. infants, children, adolescents): approx 300 per group (uncommon ADRs – 1 in 100)
- Specified risks groups in addition to any of the above (e.g. immunocompromised): approx 300 per risk group (uncommon ADRs – 1 in 100)
- LAIV: duration of viral shedding and risk to close contacts

**Post-Authorisation**

- Appropriate PhV measures or studies to address i) rare and very rare AEs; ii) emerging safety concerns in populations not studied in trials.
Seasonal influenza vaccines

Post-authorisation - Enhanced safety surveillance

• **Challenges with PhV for flu vaccines**: mass immunisation in short and fixed time each year; need for product-specific surveillance in spite of multiplicity of vaccines on the market; changes in quality spec may lead to unexpected reactogenicity; expansion of vacc programs to include new target groups.

• **AIM**: detect a potential increase in frequency or severity of expected (vs. previous season) reactogenicity (local, systemic, allergic) that may indicate a potential serious risk as exposure increases. **TIME** is key to allow for early risk mitigation.

• **3 OPTIONS** are proposed: active surveillance; passive surveillance; data mining or use of electronic health record data – yearly sustainability
Seasonal influenza vaccines

Post-authorisation - Vaccine Effectiveness (VE) studies

• **Rationale**: continuous VE monitoring due to change in vaccine composition, characterise wane of protection post-vacc, harmonise study design and generate product-specific data to gain relevant information and experience

• **Study design**: i) prospective observational study (ECDC protocol for case-control study); ii) alternatives: e.g. ECDC protocol for cohort study or screening method (VE estimation by comparison with reference group)

• **Endpoints**: depend on study design; e.g. i) I: lab-confirmed flu; II: prevention of pneumonia and hospitalisation...

• **Target population**: reflect target population for the vaccine (e.g. chronically ill and elderly for inactivated vaccines); stratification key to account for age effects in children and >65y, and sub-analysis for subjects with underlying conditions

• **Careful consideration on confounders**, e.g. healthy vaccinee effect

• **VE results** should be presented annually as soon as available.
Conclusions

• New comprehensive modular guideline on influenza vaccines to enter into force by 2016 (R-Q-C)

• Revised requirements pre-authorisation to improve evaluation of new vaccines based on experience gained and progress in scientific knowledge

• Revised requirements post-authorisation to improve monitoring of vaccines’ effect:
  
  ✓ Enhanced safety surveillance monitoring each year (started 2014-2015 season)
  ✓ Vaccine Effectiveness studies to be initiated in the coming seasons
Thank you for your attention

Further information

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Link to revised influenza guideline:

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Glossary

- LAIV: live attenuate influenza vaccine
- TBC: to be confirmed
- AEs: adverse events
- RMP: Risk Management Plan
- MA: Marketing Authorisation
- MAA: Marketing Authorisation Application
- HA: Haemagglutinin
- HI: Haemagglutinin Inhibition assay
- SRH: single-radial-haemolysis assay
- VN: virus neutralisation assay
- GMTs: geometric mean titres
- SC: seroconversion
- NA: neuraminidase
- CMI: cell-mediated immunity
- VLP: virus-like particle
- ADR: adverse drug reaction
- PhV: pharmacovigilance