Oil-in-Water Adjuvants in Pandemic Influenza

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Background

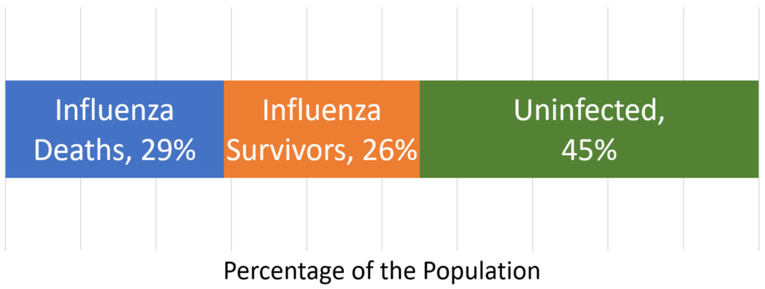
- Pandemics, caused by a marked shift in influenza subtype, may result in significant respiratory disease burden worldwide (see diagram) (1)
- Adjuvants allow use of lower dose of antigen, which is scarce at the onset of the outbreak, allowing more people to be vaccinated early
- AS03 and MF59 adjuvants were used in the 2009 swine flu (H1N1pdm09) pandemic and in testing of avian influenza vaccines, but there is only one study directly comparing their effectiveness in a pandemic (2)

Aim and Hypothesis

AIM: To determine the relative effectiveness in improving immune response, and adverse effect profile of AS03 and MF59 as adjuvants in pandemic influenza vaccines

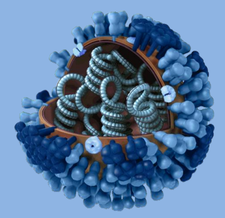
HYPOTHESIS: AS03 will be more effective than MF59, but with a worse side effect profile

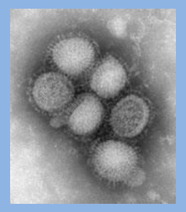
Potential Morbidity and Mortality of Pandemic Influenza. Adapted from (4,5)



Method

- A systematic review of literature in Medline and other databases including:
  - Observational and experimental studies involving the 18-64 age group
  - Studies comparing AS03-adjuvanted vaccines with unadjuvanted vaccines or unvaccinated controls; and MF59 studies with similar comparators
- Match AS03 and MF59 studies based on antigen dose
- Include studies measuring haemagglutination titre and clinical effectiveness
- Conduct an indirect-comparison meta-analysis using the R programming language using a random effects model as per the Cochrane Handbook





Strengths

- Meta-analyses provide highest levels of evidence for therapeutic guidelines (3)
- Study answers an important public health question
- Provides comprehensive literature review and,
- Provides indirect evidence of effectiveness of ASO3 vs MF59 as adjuvants

Weaknesses

- Only few studies available, and so prioritise in following order
  - Prospective, then observational studies, using clinical effectiveness
  - Experimental studies using haemagglutination titre
- Indirect rather than direct comparison
  - Match studies to minimise impact
- Potential publication bias
- Many studies funded +- run by pharmaceutical companies
  - If enough studies, conduct separate analysis of non-pharmaceutical studies
- Heterogeneous studies and study populations
  - Random effects model reduces impact

Impact

- The power of the meta-analysis may be reduced if there are too few studies, and too much heterogeneity between the studies

References

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3. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. BMC medical research methodology. 2009;9(1):34.
4. Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. Nature. 2006 Jul;442(7101):448.
5. World Health Organization. Influenza at the human-animal interface 2017. Available from: http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_06_15_2017.pdf

Images from https://www.cdc.gov/h1n1flu/images.htm