INTERNATIONAL MEETING ON INFLUENZA VACCINE EFFECTIVENESS

3-4 December 2012
Geneva
Setting

- Influenza immunization programs decades old
- Recent expansion
  - Number of programs (more countries – beyond high-income countries)
  - Target groups (even universal vaccination)
  - Vaccine types / companies
- Increased interest in measuring the value of vaccine programs
- Scientific debate on best methods to measure vaccine effectiveness
  - Concerns over study design / interpretation / confounding
  - Significant collaboration between public health partners
- Public debate/concern regarding influenza vaccine value
  - Skeptics increasingly visible / gaps in data highlighted
  - Positive efforts to provide evidence base for vaccination policies
- Need for consensus path forward
  - Best methods
  - Data gaps to fill
  - Optimal collaboration
  - Improved communication strategies
International VE Meeting

Addressing three identified needs:

• Deriving best methods for measuring VE in observational studies

• Strengthening cross-national collaborations to maximize the opportunities to address questions that can’t be answered by a single country/site

• Expanding the knowledge base and partnership to new partners that will be responsible for evaluating VE for new vaccine programs
Goals of the meeting

1. Review recent data from influenza vaccine effectiveness studies, and to map the global landscape of current VE work.

2. Discuss and agree on optimal methodologies for measuring VE, and explore best practices for conducting studies.

3. Determine critical knowledge gaps and propose a plan to address them.
   - Gaps include: methods for measurement of VE, availability data from specific target groups, settings, or for specific vaccine types.
   - Focus on identifying gaps relevant to low and mid-income countries.

4. Discuss challenges in communicating influenza vaccine effectiveness.
Meeting Agenda

Day 1

Morning
- Introduction / frame-setting
- Review of data from existing public health programs to measure VE

Afternoon
- Review of data from existing VE platforms (cont.)
- Landscape of new vaccines
- Studies from LMICs
- Start methods discussion / Critical topics

Day 2

- Formulating best practices
- Pooling of data in data repository

- VE in the elderly
- Communicating VE
- Meeting products – moving forward
Global landscape of current VE work

**Canada**
- 2 Platforms
- Canadian VE (5 provinces)
- PCIRN (Hosp) (40 sites)

**I-MOVE**
- 26 Institutes
- 17 countries

**US D.o.Defense**
- Multi-site

**US Flu VE**
- 5 sites

**Australia**
- 3 platforms -
  - VIDRL (Victoria)
  - WAIVE (W. Aust.)
  - Flu CAN (hosp.)

**VELAS**
- 5 countries
Methods of ongoing collaborations

- Mostly case-control studies
  - Test-negative control
  - Controls for health seeking behavior
  - Logistically simple
- Some cohort designs
  - Navarre (Spain); UK
- All use RT-PCR-confirmed outcomes primarily
  - With antigenic characterization of some viruses
- Multiple outcomes measured
  - MAARI, hospitalizations, ILI, deaths, pneumonia
- All feed back to national public health authorities
- All studies performed annually – with results after season
  - and sometimes interim results mid-season
Related vaccine development and efficacy activities in low and middle income countries

- Butantan - Brazil
- SII - India
- GPO - Thailand
- Vabiotech - Vietnam
- India – TIV and LAIV
- Thailand - LAIV
- Bangladesh – TIV, LAIV
- Kenya - TIV
- Senegal - TIV
- Mali, Nepal, South Africa – TIV (pregnancy)
Gaps in data

• Methodological issues:
  – Define best outcome to measure
  – Better measure total effects (direct and indirect)
  – Understand effect of prior year vaccination
  – Relationship of antigenic match & clinical protection

• VE in special groups
  – Pregnant women - optimal timing of vaccination
  – Elderly – too few quality data

• VE for PH decisions
  – Intra-season and product-specific estimates
  – Standard methods for new vaccine programs
Issues in formulating best practices

- **Choice of controls in case-control studies**
  - Test negative controls are reasonable recommendation
  - Specimen collection time (from onset) critical
    - Especially in adults and hospitalized patients
  - Systematic testing and standard case defn. critical

- **Must account for:** age, calendar time, time from illness onset, site, illness severity, frailty in analyses

- **Virus interference**
  - Hong Kong RCT noted higher risk of non-influenza viruses among children receiving vaccine.
    - Study arms had the same overall rates of respiratory illness, just from different viruses.
    - Australian data also consistent
    - US and UK data did not find this
  - ? Need for controls with no virus detected (rather than those who are influenza-negative).
Data pooling

Key issue discussed:

• How to supply public health agencies and public critical data (e.g. Summary VE for many countries, robust VE estimates by subgroups of importance) during a period of declining support?

• General interest in use of common protocol, standard case definitions, systematic testing, standard lab methods, and the same basic data collection requirements.
  – Feasibility study conducted using 3 European cohorts

• Must first define the question and scope of the collaboration
Data pooling (2)

• **Advantages**
  – Improved power and precision of VE estimates
    • Subgroups (e.g. Elderly); vaccine products
  – Shared expertise and economies of scale
  – Faster detection of VE for mid-season estimate
  – Opportunities for new research questions, including molecular markers, virus evolution, and their correlations with VE.

• **Challenges:**
  – Getting agreement on common protocol
  – Establishing agreement on timing of data receipt
  – Accounting for heterogeneity in source population, vaccine products, methodological differences (e.g. testing practices, healthcare utilization), virus circulation, etc.
  – Defining level of pooling
    • Common dataset sharing? Common protocol? Meta-analysis?
  – How to fund/support
  – Laws that prohibit international sharing of health data
Special issues – measuring VE in the elderly

- Substantial challenges to addressing biases in elderly VE estimates – historical mis-steps
- Problem of confounding in observational studies focused on non-specific outcomes (pneumonia, all-cause mortality)
  - Important confounding variables related to functional status, are not captured by ICD codes.
    - Can’t be controlled using administrative databases
  - More detail on functional impairment, including its relative severity, is needed.
    - Collect better data
      - time consuming and expensive - Canada example
  - Model the effect of functional status as a confounder and subtract that effect out of the estimates.
    - Requires multiple seasons; large number of observations
Communicating Vaccine Effectiveness

“Protection markedly lower for flu vaccine than most routinely recommended vaccines”
Vaccine is “overhyped”
• The challenge, while receipt of influenza vaccine should still be urged, is for the public to receive clear, credible, appropriate messages.
• Perceived risk is more critical than perceived benefits in the decision-making process.
• A key step - correcting risk perceptions: the actual risks of severe disease vs. the risks of severe side effects.
• Knowledge of vaccine recommendations less important
• Indirect protection has potential for pro-social behavior (getting vaccinated to protect others)
Conclusions

• **Sustainability of VE efforts in danger**
  – yearly estimates are essential
  – intra-season and product-specific estimates
  – VE studies need to identify ways to improve sustainability, including integration with existing surveillance platforms when possible, without sacrificing the quality of key required data.

• **Demonstrating VE in LMICs essential**
  – Manufacturers in LMICs expanding production
  – Need to support expanding vaccine programs

• **VE in key groups relevant to developing countries**
  – HIV infected persons
  – Pregnant women
  – Young children (malnutrition)
Expected products

• A review article on global influenza vaccine effectiveness and information gaps and plan for addressing them.

• A WHO guidance document on suggested best practices in conducting VE studies.
  – Also develop guidance for VE among elderly

• Seek consensus on pooling of data between countries

• Provide technical support to countries interested in conducting vaccine program evaluation