Perspective from industry on R&D for influenza vaccine

Giuseppe Del Giudice, Novartis Vaccines
on behalf of IFPMA IVS

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● Preamble
● R&D perspectives for improved manufacturing processes
● R&D perspectives for improved vaccine efficacy / effectiveness
● R&D perspectives for “friendly use” of vaccines
● Existing challenges
● Conclusions
The pandemic threat as a catalyst

- R&D in influenza vaccines has progressed relatively slowly until the pandemic threat of avian H5N1 flu. This represented a turning moment in the R&D for influenza vaccines both in the academic and industrial environment leading to:
  - new scientific knowledge
  - the development of new tools to improve the immunogenicity of vaccines and to allow dose sparing
  - the design of novel devices for immunization
  - new systems for vaccine manufacturing and control, etc
- All this progress has contributed to improved preparedness when the 2009 H1N1 pandemic was declared
The major areas of progress

- Preamble
- R&D perspectives for improved manufacturing processes
- R&D perspectives for improved vaccine efficacy / effectiveness
- R&D perspectives for “friendly use” of vaccines
- Existing challenges
- Conclusions
R&D perspectives for improved manufacturing processes

1. Cell-based vaccine productions

- Inactivated vaccines
  - Whole virus
  - Split virus
  - Subunit

- Live attenuated vaccines
  - Embryonated egg

- SPF embryonated egg

- MDCK
- VERO
- PER.C6

- Inactivated vaccines
  - Whole virus
  - Split virus
  - Subunit
R&D perspectives for improved manufacturing processes
1. Cell-based vaccine productions

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe use – more than 60 years of production</td>
<td>Open system, potential microbial contamination from eggs</td>
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<tr>
<td>Successful scale up to 300,000 eggs per day</td>
<td>Equipment specific to influenza production, dedicated facility</td>
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<tr>
<td>Availability of egg-based high yield viruses (reassortants)</td>
<td>Egg-adaptation might change antigen immunogenicity with respect to circulating strains</td>
</tr>
<tr>
<td>Known regulatory path</td>
<td>Intensive purification process for inactivated vaccines (ultracentrifugation)</td>
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## R&D perspectives for improved manufacturing processes

### 1. Cell-based vaccine productions

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accurate process control, closed system, thus improved aseptic operations</td>
<td>Relatively new technology for influenza vaccine with relatively new regulatory path</td>
</tr>
<tr>
<td>Elimination of egg components in the vaccine (suitable for allergies)</td>
<td>Requirement for more sophisticated equipment in cell culture processes. Cost disadvantages, not only in capital investment</td>
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<tr>
<td>Independence from eggs, avoid risk of avian retrovirus</td>
<td>Maintenance of qualified cell culture line, cell qualification requirements</td>
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<tr>
<td>Cell lines and equipment might potentially be used for a variety of vaccine products</td>
<td>Complex adventitious agents testing</td>
</tr>
<tr>
<td></td>
<td>Intensive purification process for inactivated vaccines (ultracentrifugation)</td>
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</table>

Advantages and challenges of cell-derived influenza vaccines
R&D perspectives for improved manufacturing processes
1. Cell-based vaccine production

- Vaccine virus strains closer to wild strains
- Clinical efficacy of cell-derived vaccines shown in various trials (TIV)
- Establishment of fruitful collaboration between IFPMA and CDC plus WHO Collaborating Centers to evaluate isolation of vaccine strains directly into qualified cell lines
- Large investment of US HHS for research and development of cell-based vaccines

R&D perspectives for improved manufacturing processes

2. Recombinant technologies

- These technologies have the potential to increase the overall amount of vaccine available at the end of the production process and speed up the production process itself.
- They do not depend upon influenza virus replication.
- Examples of recombinant technologies:
  - Recombinant pandemic and seasonal HA from baculovirus \(\rightarrow\) under review at FDA.
  - Recombinant VLP expressing HA, NA, M1 \(\rightarrow\) phase II.
  - Recombinant HA fused to flagellin (TLR-5 agonist) from \(E. coli\) \(\rightarrow\) phase II.
- Other approaches exist (e.g. expression in plants), but at earlier stages of development.
R&D perspectives for improved manufacturing processes
3. Potency testing of influenza vaccines

Potency of vaccines (HA content) still based on SRID

- **Pro’s** ➔ accepted method for potency by regulatory agencies / measures functionality of HA / indicates stability (sensitive to HA aggregation and denaturation)

- **Con’s** ➔ requires reagents specific for each strain / risks of delay in release due to availability of calibrated reagents / old method with high variability / labour intensive and time consuming / effects of other proteins unknown / different methods and calculations for different markets

- Need for alternative potency assays for fast, sensitive, and reproducible potency testing
R&D perspectives for improved manufacturing processes
3. Potency testing of influenza vaccines

Interim improvements to current SRID assay

• Improved robustness of calibration of reference antigens
  o Employment of new technologies/methods by ERL’s (e.g. deglycosylated SDS-PAGE, HPLC, MS).
  o Feedback data from manufacturers to be used before calibration value assigned.

• One set of reagents for each strain for all markets
  o ‘Back up’ reagents prepared by second ERL.
  o Estimates of usage rate from manufacturers to anticipate volumes required currently in progress.

• One assay method regardless of market
  o Manufacturer participation in a collaborative study to establish assay differences.
R&D perspectives for improved manufacturing processes
3. Potency testing of influenza vaccines

Alternative rapid, sensitive, and reliable assays are needed

- **HPLC**
  - Pro’s → no strain-specific reagents required / reproducible and sensitive / used for HA content in H1N1 pandemic vaccines
  - Con’s → does not measure HA functionality / does not indicate stability / does not distinguish HA’s in TIV / no common platform yet

- **SDS-PAGE**
  - Pro’s → no strain-specific reagents required / potential to estimate NA / can be specific in combination with WB / simple implementation
  - Con’s → does not measure antigenic content of HA / does not indicate stability / not suitable for trivalent vaccines
R&D perspectives for improved manufacturing processes
3. Potency testing of influenza vaccines

● ELISA
  o Pro’s → well established and easily automated methodology / sensitive / can measure functionality / suitable for trivalent vaccines
  o Con’s → still requires strain specific reagents with assigned potency

● Mass Spectrometry
  o Pro’s → readily available reference material / previously used to estimate HA content of monovalent and trivalent vaccines / distinguish Ag in presence of complex matrices / rapid, sensitive, accurate
  o Con’s → does not measure functionality of HA / does not indicate stability / complex technology

● Surface Plasmon Resonance
  o Pro’s → can measure antigenicity / automated / high accuracy, sensitivity, precision
  o Con’s → requires strain-specific reagents with assigned potency / extensive set up / single supplier
1. Adjuvants

● Industry has been pivotal in developing adjuvants for influenza vaccines

● Major effects of oil-in-water adjuvants with split and subunit influenza vaccines:
  o Dose sparing (e.g. down to 1.75-3.5 µg for pre-pandemic and pandemic vaccines)
  o Higher, and long-lasting immune response
  o Cross-protection for seasonal influenza vaccine
  o Cross-protection against different H5N1 clades
  o Enhanced efficacy and effectiveness in more susceptible subjects (e.g. children, elderly)

● Flu vaccines with oil-in-water adjuvants licensed in EU and other countries since 1997 (seasonal, MF59) and then with pre-pandemic and pandemic vaccines in many countries worldwide (AS03; MF59; AF03)
R&D perspectives for improved vaccine efficacy
2. Quadrivalent vaccines

- Improved efficacy can be achieved, not only by enhancing the immunogenicity to the three components of the existing vaccines (2 A’s and 1 B), but also by adding a second B strain.

- Quadrivalent inactivated and live attenuated influenza vaccines containing both the B/Victoria and B/Yamagata virus strains are being actively developed by all major influenza vaccine manufacturers, and are at various stage of development (phase II-phase III).
<table>
<thead>
<tr>
<th>Influenza season</th>
<th>Circulating influenza B strains [lineage]</th>
<th>Influenza B vaccine strain</th>
<th>Opposite lineage vaccine mismatch with predominant B virus</th>
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</thead>
<tbody>
<tr>
<td>2000–2001</td>
<td>B/Sichuan/379/93-like (n = 268; 89%) or B/Beijing/184/93-like (n = 33; 11%) [Yamagata]</td>
<td>B/Beijing/184/93-like [Yamagata]</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>B/Sichuan/379/99 or B/Shizuoka/15/01 (n = 61; 23%) [Yamagata]</td>
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<tr>
<td>2001–2002</td>
<td>Victoria lineage, strain not stated (n = 206; 77%)</td>
<td>B/Sichuan/379/99-like [Yamagata]</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>B/Shizuoka/15/01 [Yamagata] (n = 1; 0.5%)</td>
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<tr>
<td>2002–2003</td>
<td>B/Hong Kong/330/01-like [Victoria] (n = 268; 99.5%)</td>
<td>B/Hong Kong/330/01-like [Victoria]</td>
<td>No</td>
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<tr>
<td></td>
<td>B/Shizuoka/15/01 [Yamagata] (n = 1; 0.5%)</td>
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<tr>
<td>2003–2004</td>
<td>B/Sichuan/379/99 [Yamagata] (n = 66; 93%)</td>
<td>B/Hong Kong/330/01-like [Victoria]</td>
<td>Yes</td>
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<td></td>
<td>B/Hong Kong/330/01-like [Victoria] (n = 5; 7%)</td>
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<td>2004–2005</td>
<td>B/Shanghai/362/002-like [Yamagata] (n = 264; 74.4%)</td>
<td>B/Shanghai/362/002-like [Yamagata]</td>
<td>No</td>
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<td></td>
<td>Victoria lineage, strain not stated (n = 91; 25.5%)</td>
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<td>2005–2006</td>
<td>B/Ohio/1/005 [Victoria] (n = 261; 81.3%)</td>
<td>B/Shanghai/362/002-like [Yamagata]</td>
<td>Yes</td>
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<td></td>
<td>B/Shanghai/362/002-like or B/Florida/07/007-like [Yamagata] (n = 60; 18.7%)</td>
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<td>2006–2007</td>
<td>B/Ohio/1/005 [Victoria] (n = 254; 77%)</td>
<td>B/Malaysia/2506/04-like [Victoria]</td>
<td>No</td>
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<td></td>
<td>Yamagata lineage, strain not stated (n = 78; 23%)</td>
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<tr>
<td>2007–2008</td>
<td>[Yamagata] (n = 342; 98%), of which B/Florida/07/06-like (n = 304; 89%)</td>
<td>B/Malaysia/2506/04-like [Victoria]</td>
<td>Yes</td>
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<tr>
<td></td>
<td>B/Ohio/1/005 [Victoria] (n = 8; 2%)</td>
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<tr>
<td>2008–2009</td>
<td>B/Brisbane/60/08 [Victoria] (n = 638; 89%)</td>
<td>B/Florida/07/06-like [Yamagata]</td>
<td>Yes</td>
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<td></td>
<td>Yamagata lineage, strain not stated (n = 76; 11%)</td>
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<tr>
<td>2009–2010</td>
<td>B/Brisbane/60/08 [Victoria] (n = 27; 84.4%)</td>
<td>B/Brisbane/60/08-like [Victoria]</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yamagata lineage, strain not stated (n = 5; 15.6%)</td>
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R&D perspectives for improved vaccine efficacy
3. “Universal” vaccines

- Various approaches are pursued using conserved proteins of the virus, i.e. NP, M1, external domain of M2 (M2e), etc
- Various formulations are being used
- Development still at early stages
R&D perspectives for “friendly use” of vaccines
1. Easy administration

- Expected stronger response (targeting to professional resident antigen-presenting cell) → intradermal vaccine licensed for adults and the elderly
- Expected strong response using TIV appropriately formulated
- Possibility of self-administration
Agenda

- Preamble
- R&D perspectives for improved manufacturing processes
- R&D perspectives for improved vaccine efficacy / effectiveness
- R&D perspectives for “friendly use” of vaccines
- Existing challenges
- Conclusions
Existing challenges. 1

Need to increase coverage with influenza vaccines

- Influenza vaccines developed with new technologies need to reach the people (the vaccine needs to become vaccination)
- For 2009-2010 influenza season, in the USA 41% coverage estimated for the seasonal vaccine (6 mo or older) and 27% estimated for the pandemic vaccine.
- Even coverage of elderly is far from optimal
- It becomes important that the public sector makes more effort to recommend and implement influenza vaccination in a larger segment of the population (e.g. Increase awareness, education, etc)

Vaccination of at risk <65s is considerably lower than the elderly


Existing challenges. 2

High research and development costs

- Investments in discovery research
- Large and long clinical trials
- Construction of dedicated influenza vaccine production facilities
- Need for industry to consider appropriate returns and for public sectors to participate in the R&D costs (ex. HHS and DOD in the USA) and to support higher prices of the new products
Regulatory challenges

- Influenza vaccines prepared with new technologies face new regulatory issues that need proactive guidance and an appropriately prepared “scientific regulatory” environment.

- In Europe, strains obtained with reverse genetics are classified as GMO → need for Centralized Procedure instead of Member State Mutual Recognition.

- Increasing requirements for efficacy data and the lack of suitable correlates of protection for some vaccines (e.g. LAIV) and for some age groups (e.g. children) creates complexity and uncertainties.

- Lack of proactive recommendations for pandemic preparedness.
Agenda

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Conclusions

● Industry is playing a key and active role in changing the landscape of influenza vaccine development with the ultimate objective of:
  o making vaccine available for a larger sector of the population worldwide (more production, dose sparing, etc)
  o making seeds faster and speeding release assays
  o rendering the vaccines more efficacious and more “user-friendly” used

● New and improved vaccines have already been successfully introduced (e.g. adjuvants, cell-derived vaccines, intradermal vaccines, etc). Their use is expected to be extended in the next few years especially in populations at risk

● Other influenza vaccines are in sight, such as the quadrivalent inactivated vaccines containing two B virus strains

● The development of “universal” vaccines covering all drifted and shifted virus strains is very promising, but will require more research. Their development will represent a breakthrough

● The novel perspectives in influenza vaccine R&D still face challenges at the level of vaccination coverage, costs, and regulatory that need a open and constant dialogue with regulatory agencies and public sectors
Thank you