The Veterinary Biological Industry and the Production of Human Pandemic Influenza Vaccines in Mexico

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Avimex*
Avimex*

- Leading veterinary pharmaceutical and biological company in Mexico.
- It is 100% Mexican owned
- Primary focus: poultry
- Strong R&D activity in avian influenza vaccines
- Currently produces an H5N2 oil-emulsified vaccine that has been in use in Mexico for over 10 years
- Avimex* exports the AI H5N2 vaccine to Japan, Taiwan, Indonesia, Jordan, Nigeria, Bielorus, Egypt, Guatemala, El Salvador.
The problem

Human pandemic influenza outbreak

• There will be no vaccine available for everybody:
  – Not enough chicken embryos
  – Large amount of doses needed for humans
  – A limited number of human influenza (HI) vaccine producers: annual capacity of only 350M doses

• Different scenarios: if H5 affects humans (not the case so far) or H3 or H1 (current situation) or H7 and H9.
The question??

Can veterinary vaccine production facilities in Mexico produce human pandemic influenza vaccines?
Yes, but depending on:

- Individual producers decision
- The timing and the scenarios of H5 or H3, H1 or H7, H9 outbreak
- Financial support, supply of technology and regulatory requirements
The option

Veterinary vaccine producers (VVP)

• Among various strategies to prevent and control a human influenza pandemic is the production of a human influenza vaccine in suitable veterinary manufacturing facilities
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Background

Avian Influenza in Mexico

• In autumn of 1993 first presence of LPAI
• May 23, first official recognition of LPAIV
  – No vaccination, but half of the country was infected
  – Official Campaign for AI at the beginning: stamping out, etc.
  – Development of a vaccine was decided by SAGARPA and INFARVET.
• December 19, first outbreak of HPAI
  – Vaccination was decided
Background

Avian Influenza in Mexico

• After February 1995 no HPAIV was isolated in Mexico
• June 1995, Mexico declared to OIE to be free of HPAI
• Since then Mexico is using vaccination for controlling LPAIV to prevent the risk of virus mutation.
• Nowadays no HPAIV has been isolated.
Background

Health Principle

• Our position as AI vaccine producer is very clear:

  Our primarily responsibility is to the poultry industry,
  
  But we can not disregard

  Human health
To preserve and promote animal health in order to preserve human health.

The strategy is to control bird flu at its origin, in affected countries.

Our focus is to control AI in birds first with an appropriate tool: the AI vaccine.

If we control AI in birds, the chances of a pandemic in humans will be reduced.
AI vaccine

Vaccine development

• Mexican government with the poultry biological industry (Infarvet) developed an oil-emulsion vaccine in 1994.
• Poultry vaccine producers had previous knowhow in oil-emulsion vaccines,
• Derived from an apathogenic (LP) strain of the subtype H5N2 of AI.
• 100% protection is achieved, 15 days post vaccination when challenged with an HPAIV.
AI vaccine

Official veterinary regulations

• SAGARPA initially inspected the facilities of 4 veterinary vaccine facilities to approve them.
• NOM 055 regulates the production and distribution of AI vaccine.
• The MS (master seed) is owned by the government and the PS (production seed) is sold to approved laboratories only.
• All safety tests for chickens were initially performed by the government, now by the approved labs.
Testing of the MS and PS were regularly performed to ensure their integrity and quality.

Immunogenicity tests are performed by production labs on all batches to ensure compliance with Mexican government regulations (higher than current OIE regulations).

Potency (challenge) tests are conducted by the government (up to now).
• The MS (master seed) is owned by government and only the PS (production seed) is sold to the approved veterinary vaccine producers.

• Emulsified inactivated vaccine, produced in chicken embryos

• Contains at least 16% of crude antigen of $10^{8.0}$ CEID50%ml or 0.5 mcg of protein per bird.
Manufacturing plants

Four main Government Approved AI vaccine producers

- Avimex
- Boehringer
- IASA
- Intervet
Manufacturing plants

Capacity

• Estimated capacity of this four laboratories is around 500,000 bottles a month (500M doses)
• This capacity, if entirely allocated to human vaccine production, can produce 100M doses in four months (15 mcg per dose)
• The capacity in 6 months could be expanded to 1.0B doses
• The problems:
  • Availability of chicken embryos
  • Protective dose for humans (90 mcg?)
Quality assurance

• Veterinary vaccine producers fulfill the Mexican GMP requirements
• The four approved producers exceed this norm.
• The biosecurity level (BSL) required is normally level 2 (H5N2 does not infect humans).
• The H5N2 vaccine produced in Mexico is effective against H5N1 in chickens.
Example of a Production Plant
1st Candling  
Inoculation  
Incubators  
2nd Candling

Labeling  
Filling  
Emulsion  
Harvest

Sanitation  
Cool Room

View Area
View area
First candling
Inoculation process
Incubation
Second candling
Cool room
Sanitation process
Harvesting process
Emulsification process
First Conclusion

- The Mexican veterinary vaccine production facilities **could be used**, under certain circumstances, for the production of human pandemic vaccines due to:
  - Existing expertise in the production of AI antigen
  - Facilities that can fulfill human vaccine production standards
  - Highly qualified technicians in vaccine production
Vet facilities for production of HPIV?

The most important question

What should be the **strategy** for this option, under different **scenarios** (H5 or others) and **timing** to produce a pandemic human influenza vaccine?
Strategy H5 vs H?

Scenarios for a round table discussion

• **Scenario 1:**
  • H5 pandemic influenza virus in humans (PIVH) in a short time (within one year)

• **Scenario 2:**
  • The PIVH appears with another HA (H3, H1,)

• **Scenario 3:**
  • The PIVH with any other HA (H7 or H9)

• **Scenario 4:**
  • New HA?
Strategy for Scenario 1

H5 pandemic in humans

• Consideration #1: H5N2 as a vaccine
• Today we produce H5N2 that is 100% effective against H5N1 in birds.
• If H5 affects humans, this H5N2 antigen can be used in a human vaccine because:
  • Apathogenic for humans (up-to-date)
  • Expertise in handling the virus
Strategy for Scenario 1

H5 pandemic in humans

• Support will be needed only for:
  • Purification of virus
  • Formulation of final product
  • Quality test for releasing the product to the market
  • Regulatory compliance
  • Mock up vaccine (H5N2)
Strategy for Scenario 1

H5 pandemic in humans

• Consideration #2: H5N1 as a vaccine.
• Using the H5N1 virus or another NA (the one that will prevail)
• We think a reverse engineering virus for making it less pathogenic for humans would be convinient (workers)
• We could use the same production outline as for H5N2.
Strategy for Scenario 1

H5 pandemic in humans

- Support needed for:
  - Purifications methods
  - Formulation of final product
  - Quality test for releasing the product to the market
  - Vaccine against H5N1 for our workers
  - Regulatory compliance
  - Mock up vaccine
Strategy for Scenario 1

H5 pandemic in humans

- Consideration #3:
- Using a live virus
  - Could be H5N2 or H5N1
  - Low pathogenicity
  - Reverse genetics?
  - Others
Strategy for Scenario 1

H5 pandemic in humans

- Consideration #4:
- Veterinary vaccine producers can contribute with specific supplies:
- Allantoic fluids
Strategy for Scenario 2

H3,H1 pandemic in humans

• **Consideration #1**: In the short range
  We could use the same procedures used for H5N2 AI vaccine production.
Strategy for Scenario 2

H3, H1 pandemic in humans

• Support would be needed for:
  • Purification methods
  • Formulation of final product
  • Quality test for releasing the product to market
  • Vaccine for our workers
• New technologies
• Regulatory and financial
Strategy for Scenario 3

H7 or H9 pandemic in humans

• **Consideration #1**: In the short range
  We could use the same procedures used for H5N2 AI vaccine production.
Strategy for all Scenarios

Delayed occurrence of human pandemic (4 years+)

• Suggestions:
  • New technologies needed:
    • Recombinant vaccines
    • Peptide vaccines
    • New substrates for production
Vet facilities for production of HPIV?

Second conclusion

• Short term (within one year) Veterinary Labs can immediately support Human Labs in the production of HPIV if H5 is the prevailing pandemic virus due to:
  • Existing knowledge of the H5 strain.....
Vet facilities for production of HPIV?

...Second conclusion

- In the *middle and long term with other HA*, Vet facilities can eventually be used, but with support in:
  - Production technologies
  - Regulatory
  - Financial
First Conclusion

• The Mexican veterinary vaccine production facilities could be used, under certain circumstances, for the production of human pandemic vaccines due to:
  • Existing expertise in the production of AI antigen
  • Facilities that can fullfill human vaccine production standards
  • Highly qualified technicians in vaccine production
New questions?

- What are the **main differences** between Avian Influenza Vaccines currently on the market and Human Influenza Vaccines?
- What **immediate action** is needed?
Main differences

Immediate actions

• Today:
  • Strain
  • Purification
  • Formulation
  • Release of the product
  • Regulatory aspects
  • Faster quality control, especially on the production seed.
Summary

- Approved Mexican AI vaccine producers meet OIE standards for manufacturing AI vaccines.
- Their facilities can fulfill human vaccine production requirements.
- In the short term (within one year), in case of an H5 pandemic emergency, these laboratories are a suitable option for a pandemic human vaccine production.
Summary

Decision and appropriate actions to use these facilities for a pandemic human influenza vaccine production must be eminent, backed with technological, financial and regulatory support, depending on the different scenarios and timing of the pandemic.