

**Symposium Keynote Address—

**Impact of Vaccines and Vaccination on Global Control of Avian Influenza**

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**SUMMARY.** There are 30 recorded epizootics of H5 or H7 high pathogenicity avian influenza (HPAI) from 1959 to early 2012. The largest of these epizootics, affecting more birds and countries than the other 29 epizootics combined, has been the H5N1 HPAI, which began in Guangdong China in 1996, and has killed or resulted in culling of over 250 million poultry and/or wild birds in 63 countries. Most countries have used stamping-out programs in poultry to eradicate H5N1 HPAI. However, 15 affected countries have utilized vaccination as a part of the control strategy. Greater than 113 billion doses were used from 2002 to 2010. Five countries have utilized nationwide routine vaccination programs, which account for 99% of vaccine used: 1) China (90.9%), 2) Egypt (4.6%), 3) Indonesia (2.3%), 4) Vietnam (1.4%), and 5) Hong Kong Special Administrative Region (<0.01%). Mongolia, Kazakhstan, France, The Netherlands, Cote d’Ivoire, Sudan, North Korea, Israel, Russia, and Pakistan used <1% of the avian influenza (AI) vaccine, and the AI vaccine was targeted to either preventive or emergency vaccination programs. Inactivated AI vaccines have accounted for 95.5% of vaccine used, and live recombinant virus vaccines have accounted for 4.5% of vaccine used. The latter are primarily recombinant Newcastle disease vectored vaccine with H5 influenza gene insert. China, Indonesia, Egypt, and Vietnam implemented vaccination after H5N1 HPAI became enzootic in domestic poultry. Bangladesh and eastern India have enzootic H5N1 HPAI and have not used vaccination in their control programs. Clinical disease and mortality have been prevented in chickens, human cases have been reduced, and rural livelihoods and food security have been maintained by using vaccines during HPAI outbreaks. However, field outbreaks have occurred in vaccinating countries, primarily because of inadequate coverage in the target species, but vaccine failures have occurred following antigenic drift in field viruses within China, Egypt, Indonesia, Hong Kong, and Vietnam. The primary strategy for HPAI and H5/H7 low pathogenicity notifiable avian influenza control will continue to be immediate eradication using a four-component strategy: 1) education, 2) biosecurity, 3) rapid diagnostics and surveillance, and 4) elimination of infected poultry. Under some circumstances, vaccination can be added as an additional tool within a wider control strategy when immediate eradication is not feasible, which will maintain livelihoods and food security, and control clinical disease until a primary strategy can be developed and implemented to achieve eradication.

**RESUMEN.** *Estudio recapitulativo por invitación—* Impacto de las vacunas y la vacunación para el control global de la influenza aviar.

Se han presentado 30 epizootias de la influenza aviar de alta patogenicidad H5 o H7 de 1959 a principios del año 2012. La mayoría de estas epizootias, que ha afectado más aves y países en comparación con las otras 29 epizootias combinadas, ha sido la influenza aviar altamente patógena H5N1, que comenzó en Guangdong, China, en 1996 y que causó la muerte o la eliminación de más de 250 millones de aves de corral y/o aves silvestres en 63 países. La mayoría de los países han utilizado los programas de sacrificio sanitario en aves de corral para erradicar la influenza aviar altamente patógena H5N1. Sin embargo, 15 países afectados han utilizado la vacunación como parte de la estrategia de control. Más de 113 millones de dosis fueron utilizadas desde 2002 al 2010. Cinco países han utilizado programas rutinarios de vacunación en todo el país, que representan el 99% de las vacunas utilizadas: 1) China (90.9%), 2) Egipto (4.6%), 3) Indonesia (2.3%), 4) Vietnam (1.4%), y 5) Hong Kong, Región Administrativa Especial (<0.01%). Mongolia, Kazajstán, Francia, Holanda, Costa de Marfil, Sudán, Corea del Norte, Israel, Rusia y Pakistán han utilizado menos del uno por ciento de la vacuna contra influenza aviar y la vacunación fue dirigida a programas de vacunación preventiva o de emergencia. Las vacunas inactivadas contra la influenza aviar han representado el 95.5% de las vacunas utilizadas y las vacunas con virus vivos recombinantes han representado el 4.5% de las vacunas utilizadas. Estas últimas son principalmente la vacuna recombinante que utiliza el virus de la enfermedad de Newcastle como vector con un inserto del gen H5 del virus de la influenza aviar. China, Indonesia, Egipto y Vietnam implementaron la vacunación después que la influenza aviar de alta patogenicidad H5N1 se convirtió en enzootica en aves domésticas. Bangladesh y la India oriental tienen influenza aviar de alta patogenicidad H5N1 enzootica y no han utilizado la vacunación en sus programas de control. La enfermedad clínica y la mortalidad se han prevenido en los pollos, los casos en humanos se han reducido, y los medios de subsistencia rurales y la seguridad alimentaria se han mantenido mediante el uso de vacunas durante los brotes de influenza aviar altamente patógena. Sin embargo, brotes de campo se han producido en los países donde se ha llevado a cabo la vacunación, sobre todo debido a la insuficiente cobertura de las especies objetivo, se han producido fracasos en la vacunación después de cambios por derivación antigenica de los virus de campo en China, Egipto, Indonesia, Hong Kong y Vietnam. La estrategia principal de control para la influenza aviar de alta patogenicidad y de baja patogenicidad H5/H7 de declaración obligatoria continúa siendo la erradicación inmediata utilizando una estrategia de cuatro componentes: 1) educación, 2) bioseguridad, 3) el diagnóstico rápido y vigilancia, y 4) la eliminación de aves infectadas. En algunas circunstancias, la vacunación se puede agregar como una herramienta adicional dentro de una estrategia más amplia de control cuando la erradicación inmediata no es factible, la que mantendrá los medios de subsistencia y la seguridad alimentaria, y controlará a la enfermedad clínica hasta que una estrategia primaria pueden ser desarrollada e instrumentada para lograr la erradicación.

Key words: avian influenza, highly pathogenic avian influenza, vaccination, vaccine

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HIGH PATHOGENICITY AVIAN INFLUENZA EPIZOOTICS AND CONTROL

Since identification of influenza A virus as the cause of fowl plague or high pathogenicity avian influenza (HPAI) in 1955, 30 epizootics of HPAI in birds have occurred around the world (Table 1) (30). Traditional control strategies for HPAI have relied upon four basic categories of components: 1) education (including behavioral change communications), 2) biosecurity (including modifications to the ways in which poultry are reared and sold, movement management, and cleaning and disinfection), 3) diagnostics and surveillance, and 4) elimination of infected poultry, usually through culling or depopulation (30). In 1995, a fifth category was added, decreasing host susceptibility, with the field implementation of vaccines and vaccination in Mexican and Pakistani control programs. In the future, increasing host resistance through genetics may replace or at least augment vaccination as a means to decrease host susceptibility.

Of the 30 HPAI epizootics, 28 have involved single countries, and two have involved multiple countries (1996–present, H5N1 in 63 countries of Asia, Europe, and Africa; and 2003, H7N7 in The Netherlands, Belgium, and Germany) (30). The number of birds affected ranges from 1300 to over 250 million (Fig. 1). This number is quite small considering over 58 billion poultry are raised per year in the world. Most of the epizootics were short, spanning <1 yr, and most were addressed using a comprehensive control program involving stamping-out, which led to eradication (Fig. 2). However, four epizootics used vaccines and vaccination as a part of the control strategies: 1) Mexico, H5N1, 1994–95 (32); 2) Pakistan, H7N3, 1995–2004 (16); 3) Asia/Africa/Europe, H5N1, 1996–continuing (24,29); and 4) North Korea, H7N7, 2005 (17). These four epizootics used vaccination as an added control component because either traditional stamping-out programs did not eradicate the disease, or resources were not available or were inadequate to accomplish eradication. In these situations, vaccination was used as a tool to reduce infection pressure while maintaining rural livelihoods and food security, controlling the clinical disease, and allowing development of infrastructure that could lead to eradication.

There is no “one control strategy” for HPAI eradication (30). The H5N1 HPAI panzootic that emerged in 1996 in China is unique because of the 16 yr of reported outbreaks, 9 yr of multicountry control experience (2003–12), multiple introductions into some countries with multiple eradications, and wild bird involvement. There have been several quantifiable successes, including eradication in 57 countries, reduction in number of outbreaks in poultry, reduction in the time to eradication, reduction in rate of human cases in countries with adequate surveillance, and the refinement of the role of vaccines and vaccination as tools in a comprehensive control program. In addition, we must ask ourselves, “What did the 57 countries that eradicated H5N1 HPAI do that was ‘right’?” Their control strategies had sufficient application of each of the four components (education, biosecurity, diagnostic and surveillance, and elimination of infected poultry) to achieve eradication. If the other countries have not achieved eradication using the same four components, then what will the addition of vaccines and vaccination to the control strategy do? In experimental studies, vaccines and vaccination have been shown to increase resistance to virus infection, reduce virus replication in respiratory and gastrointestinal tracts, and prevent illness and death in poultry. In the field, these aspects will reduce environmental contamination by the virus (12,18), reduce transmission to birds, as has been demonstrated experimentally (4,13), reduce human exposure and infections (18,29), and maintain livelihood and food security of rural poor (18). However, vaccines and vaccination cannot eradicate HPAI; i.e., eradication can only be achieved through a comprehensive strategy coordinating vaccines and vaccination with the other four control components.

There have been some reports of AI vaccine “failures” in the field with cases of HPAI in four countries with enzootic infection that vaccinate, and isolation of H5N1 and/or identification of disease clinically consistent with HPAI in vaccinated flocks (14,27,31). Statements about the cause of these vaccine “failures” in HPAI field control are short on facts and long on speculations. What is the true situation in the field? What can we learn by digging deep into individual countries? OFFLU, the joint OIE and FAO animal influenza network of experts, conducted an evaluation of global avian influenza control strategies for poultry, especially AI vaccine and vaccination components, during 2010–11 (21,29). The evaluation of HPAI control programs was divided into three levels: 1) overall economic condition of the countries, along with functionality of their veterinary services and poultry density, 2) international comparisons of HPAI control programs, and 3) detailed examination of the application of the HPAI control program within individual countries.

**General economic, agricultural, and veterinary services impact of control.** The initial study compared HPAI control against a elimination of infected poultry) to achieve eradication. If the other

**Abbreviations:** AGDP = agricultural gross domestic product; AI = avian influenza; FAO = Food and Agriculture Organization; GDP = gross domestic product; GNI = gross national income; HDI = human development index; HPAI = high pathogenicity avian influenza; LP = low pathogenicity; LPNAI = low pathogenicity notifiable avian influenza; OECD = Organization for Economic Cooperation and Development; OIE = World Organization for Animal Health; OFFLU = OIE and FAO animal influenza network; PVS = OIE Performance of Veterinary Services evaluation
poultry density is offset by improved biosecurity practices to reduce transmission. However, with intracountry analysis by region, province, or county, high poultry density even in developed countries may prolong outbreaks (26). There was no significant association between HPAI outbreak data and the economic indicators of GDP, AGDP, % AGDP, GDP/capita, GNI, and HDI (21). However, OECD membership was associated with shorter and significantly fewer HPAI outbreaks, quicker eradication times, lower reported mortality rates (compared to at-risk susceptible poultry), and higher culling rates than non-OECD member countries. OECD members not only have high-income economies, but they also require governmental transparency and good governance.

The role of national, provincial, and local veterinary services in control of animal diseases is critical in implementing policy. OIE has developed and implemented the PVS tool, which evaluates the function of critical competencies of a country’s veterinary services. For this study, core competencies were evaluated against HPAI outbreak data for staffing of veterinarians and other professionals, quicker eradication times, lower reported mortality rates (compared to at-risk susceptible poultry), and higher culling rates than non-OECD member countries. OECD members not only have high-income economies, but they also require governmental transparency and good governance.

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In general, these data emphasize that lower critical competencies of veterinary services are associated with poorer AI outbreak control, as is evident by greater numbers of HPAI outbreaks, the longer

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Subtype</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959</td>
<td>Scotland</td>
<td>H5N1</td>
<td>Chickens (<em>Gallus gallus domesticus</em>)</td>
</tr>
<tr>
<td>1961</td>
<td>South Africa</td>
<td>H5N3</td>
<td>Common terns (<em>Sterna hirundo</em>)</td>
</tr>
<tr>
<td>1963</td>
<td>England</td>
<td>H7N3</td>
<td>Turkeys (<em>Meleagris gallopavo</em>)</td>
</tr>
<tr>
<td>1966</td>
<td>Canada</td>
<td>H5N9</td>
<td>Turkeys</td>
</tr>
<tr>
<td>1975</td>
<td>Australia</td>
<td>H7N7</td>
<td>Turkeys and ducks (<em>Anas platyrhynchos</em>)</td>
</tr>
<tr>
<td>1979</td>
<td>Germany</td>
<td>H7N7</td>
<td>Chickens and geese (<em>Anser anser domesticus</em>)</td>
</tr>
<tr>
<td>1979</td>
<td>England</td>
<td>H7N7</td>
<td>Turkeys</td>
</tr>
<tr>
<td>1983–84</td>
<td>USA</td>
<td>H5N2</td>
<td>Chickens, turkeys, partridges (<em>Alectoris chukar</em>), guinea fowl (<em>Numida meleagris</em>), and miscellaneous poultry</td>
</tr>
<tr>
<td>1983</td>
<td>Ireland</td>
<td>H5N8</td>
<td>Turkeys, chickens, ducks</td>
</tr>
<tr>
<td>1985</td>
<td>Australia</td>
<td>H7N7</td>
<td>Chickens</td>
</tr>
<tr>
<td>1991</td>
<td>England</td>
<td>H5N1</td>
<td>Turkeys</td>
</tr>
<tr>
<td>1992</td>
<td>Australia</td>
<td>H7N3</td>
<td>Chickens, ducks</td>
</tr>
<tr>
<td>1994</td>
<td>Australia</td>
<td>H7N3</td>
<td>Chickens</td>
</tr>
<tr>
<td>1994–95</td>
<td>Mexico</td>
<td>H5N2</td>
<td>Chickens</td>
</tr>
<tr>
<td>1995 &amp; 2004</td>
<td>Pakistan</td>
<td>H7N3</td>
<td>Chickens</td>
</tr>
<tr>
<td>1996–cont.</td>
<td>Asia, Africa, Europe</td>
<td>H5N1</td>
<td>Various poultry and wild birds</td>
</tr>
<tr>
<td>1997</td>
<td>Australia</td>
<td>H7N4</td>
<td>Chickens, emus (<em>Dromaius novaehollandiae</em>)</td>
</tr>
<tr>
<td>1997</td>
<td>Italy</td>
<td>H5N2</td>
<td>Various poultry</td>
</tr>
<tr>
<td>1999–2000</td>
<td>Italy</td>
<td>H7N1</td>
<td>Chickens, turkeys, guinea fowl, quail, ducks, pheasants, ostriches (<em>Struthio camelus</em>)</td>
</tr>
<tr>
<td>2002</td>
<td>Chile</td>
<td>H7N3</td>
<td>Chickens, turkeys</td>
</tr>
<tr>
<td>2003</td>
<td>Netherlands, Belgium, Germany</td>
<td>H7N7</td>
<td>Chickens and various other poultry</td>
</tr>
<tr>
<td>2004</td>
<td>USA</td>
<td>H5N2</td>
<td>Chickens and various other poultry</td>
</tr>
<tr>
<td>2004</td>
<td>Canada</td>
<td>H7N3</td>
<td>Chickens</td>
</tr>
<tr>
<td>2004 &amp; 2006^</td>
<td>South Africa</td>
<td>H5N2</td>
<td>Ostriches and various other poultry</td>
</tr>
<tr>
<td>2005</td>
<td>Peoples’ Republic of Korea</td>
<td>H7N7</td>
<td>Chicken</td>
</tr>
<tr>
<td>2007</td>
<td>Canada</td>
<td>H7N3</td>
<td>Chickens</td>
</tr>
<tr>
<td>2008</td>
<td>England</td>
<td>H7N7</td>
<td>Chickens</td>
</tr>
<tr>
<td>2009</td>
<td>Spain</td>
<td>H7N7</td>
<td>Chickens</td>
</tr>
<tr>
<td>2011–cont.</td>
<td>South Africa</td>
<td>H5N2</td>
<td>Ostriches</td>
</tr>
<tr>
<td>2012–cont.</td>
<td>Chinese Taipei</td>
<td>H5N2</td>
<td>Chickens</td>
</tr>
</tbody>
</table>

Additional studies are needed to determine if these are two distinct lineages for the hemagglutinin genes of these H5N2 viruses. In this table, they are grouped together as one lineage of virus.
**Fig. 1.** Number of birds that died or were culled for HPAI in the 30 reported epizootics from 1959 to early 2012. Lack of visible bar indicates <1 million birds.

**Fig. 2.** Time line for the 30 reported HPAI epizootics from 1959 to early 2012.
duration of outbreaks, and higher mortality rates. Interestingly, the link between competencies of veterinary services, including emergency funding, and control of HPAI corroborates previous analyses emphasizing that adequate finances and good governance, as espoused in OECD membership, are essential for functionality in animal disease control.

**International comparisons of HPAI control programs.** An assessment of the specific components in AI control programs for countries that reported HPAI and/or H5/H7 low pathogenicity notifiable avian influenza (LPNAI) outbreaks during 2002–10 was accomplished (29). Sixty-nine of 80 countries completed and returned a questionnaire (86%) on their national HPAI and H5/H7 LPNAI control programs. Responding countries were from six continents: Asia (n = 24), Africa (n = 10), North America (n = 5), South America (n = 1), Europe (n = 28), and Australia/Oceania (n = 1). Of the 69 countries, 27 countries (39%) had HPAI outbreaks in poultry, 11 countries (16%) had HPAI outbreaks in wild birds, 26 countries (38%) had HPAI outbreaks in both poultry and wild birds, and five countries (7%) had H5/H7 LPNAI outbreaks in poultry. In addition, 14 (20%) of the 69 countries had both HPAI and H5/H7 LPNAI outbreaks in poultry. All 69 countries had national HPAI and H5/H7 LPNAI control programs. These programs had many common components, including: quarantine and additional movement restrictions or controls, tracing of poultry in the outbreak area, enhanced biosecurity measures, farmer and public education and awareness about the disease, monitoring, rapid diagnostics, stamping-out of positive cases, disinfection of facilities and equipment, decontamination and disposal of infectious materials, and compensation. Some countries had more detailed and tailored plans that also included additional components, such as crisis management framework, high-throughput rapid diagnostic testing, early processing of at-risk noninfected poultry, emergency vaccination, pen-side testing as a screening tool, and zoning of movement restrictions and surveillance. The practice of eliminating infected poultry varied with country. For HPAI, some countries practiced culling only on the infected premises, while with others, culling also included dangerous contacts and contiguous premises. With some countries, a zonal approach was used of culling all poultry within 0.5, 1, or 3 km of the infected premises. With AI control programs in some countries, alternatives for elimination of poultry infected with H5/H7 LPNAI were used, including marketing of recovered birds, but most elected to cull infected poultry. The quantitative implementation of each component varied with individual country, resulting in variations in the speed of eradication.

Fifty-eight percent of countries specified a vaccination option for HPAI, while only 39% had vaccination as an option in H5/H7 LPNAI control strategies. Vaccination can be used in three ways: as a preventive tool when risk of introduction is high, or as an emergency action after an outbreak begins, or as a routine measure when infection is enzootic within the country. However, for an emergency vaccination program to be effective, a vaccine bank, field trials, and a vaccination implementation plan in the field need to be in place before the emergency occurs. Fifty-eight percent of the countries had written plans with specific vaccine and vaccination use criteria, but only 14% had completed AI vaccine and vaccination simulation exercises or worked out the logistics of implementing a vaccination program. Field trials for vaccine efficacy had been conducted by 25% of the countries for H5, and 7% of the countries for H7 vaccines. Thirty percent of countries had used vaccines for HPAI control; 16% of countries used it in poultry, only 10% used it in collections of captive birds, and 4% used it in both poultry and bird collections. For H5/H7 LPNAI control, 12% of countries used vaccines. Non-H5/H7 LPNAI vaccines were used in 17% of countries, where H9N2 was the most common and was used in 10 countries. However, some vaccines have been used to control H1 and H3 swine influenza viruses in turkeys in Canada and the United States, H6 AI viruses in poultry in Germany, South Africa, and the United States, and H2 and H4 AI viruses in poultry in the United States (3,29).

Vaccine banks have been an important part of preparation for emergency vaccination programs. Ten countries had vaccine banks containing H5 vaccines, and three countries had both H5 and H7 vaccines in their banks. The quantity of vaccines ranged from 0.5 to 55 million doses per subtype, but most countries had ≤3.5 million doses per subtype. The vaccines were acquired in 2006 (n = 4), 2007 (n = 1), 2008 (n = 1), 2009 (n = 1), and 2010 (n = 3), or were not specified. Expiration dates of vaccines ranged from 1 to 4 yr. As vaccines expired, countries have identified two main options for the future: rotating stocks from commercial vaccine manufacturers or opting out of vaccine banks because of perceived decrease in risk for HPAI or H5/H7 LPNAI introduction. Most countries have concluded that maintaining government-held vaccine banks has too high a cost-benefit ratio.

The H5/H7 AI vaccines have been used in six different types of programs: 1) zoo and captive-held nonpoultry, 2) single poultry farms, 3) ring vaccination of poultry around AI outbreaks, 4) targeted vaccination of high-risk poultry, 5) targeted vaccination of specific sectors of poultry, and 6) routine vaccination of poultry. First, a large program funded by the European Union conducted vaccination on zoo birds and captive-held nonpoultry in 13 countries. In addition, seven other countries had vaccination programs for such bird populations (29). Second, single poultry farms conducted vaccination programs in poultry. Examples include the 2003–04 vaccination of layers in a single company of Connecticut (USA) layers for H7N2 LPNAI and the 2006 vaccination of ostriches on a single Israeli farm for H5N1 HPAI (29). Third, ring vaccination has been practiced in poultry around H7N3 outbreak zones in Pakistan since 2004 (29). Fourth, vaccination was targeted for high-risk poultry such as outdoor ducks in France during 2006 and free-range layers in the Netherlands from 2006 to 2008, but such vaccinations were a small percentage of susceptible poultry (29). Fifth, vaccination was focused to specific sectors of poultry, such as turkeys and capons in northern Italy from 2003 to 2005 for H7N3 and/or H5N2 LPNAI (5,15,29). Sixth, routine vaccination of all poultry within a country either as a campaign or age-dependent strategy as has occurred in China, Egypt, Vietnam, and Indonesia against H5N1 HPAI since 2002 (29). In addition, Mexico also has continued a routine vaccination program for H5N2 LPNAI in chickens since 1995 (32,33).

From the survey, the top five reasons cited for not using H5/H7 vaccines were absence of notifiable AI in the country, no immediate risk for notifiable AI outbreaks, successful stamping-out campaigns, the lack of adequate resources for vaccination, and the high cost of vaccines. By comparison, the reasons for using vaccines, as indicated by the survey, by countries that are using, have used, or may use H5/H7 vaccines include stamping-out measures were not adequate in large outbreaks, to control localized infection “persistent” in some population of poultry species (i.e., domestic ducks), to protect expensive breeds and birds, the presence of enzootic disease, and availability and adequacy of vaccination resources.

A common question concerning vaccination is whether vaccination created H5N1 HPAI enzootic status? This is best answered by examining individual countries. For Bangladesh and eastern India, H5N1 HPAI has become enzootic without AI vaccination. In Egypt, 383 outbreaks occurred before vaccination was initiated, and 573
outbreaks occurred before 1% of the poultry population had been vaccinated (6,11). In China, the first H5N1 cases were reported in 1996 in published literature, but no official outbreaks were reported to OIE until 2004, when China received OIE membership. During the first two months of 2004, 48 outbreaks occurred in 16 provinces throughout the whole country (i.e., H5N1 HPAI cases in the northern, southern, western, and eastern provinces of China), while vaccination for mainland China did not begin until after the 2004 outbreaks (8,9,19). For Indonesia, vaccination began mid-2004, but the first cases of H5N1 HPAI occurred in July 2003, with 312 outbreaks and 10.9 million deaths by June 2004 (19,23). Vaccination in Vietnam did not start until October 2005, but by the end of 2004, 24% of communes and 60% of towns had cases, with 17% of the poultry population being affected (19,25). These data suggest that H5N1 HPAI was enzootic before vaccination was effectively applied (29).

Vaccine usage for HPAI has varied by year, with initial implementation in 2002 in Hong Kong (Fig. 3) (29). Usage increased in 2003 with full implementation of vaccination in Hong Kong. Usage jumped in 2004 with initiation of vaccination in China and Indonesia, but the demand in China alone was greater than the manufacturing capacity, and manufacturing was only expanded sufficiently to meet the demand in 2006. The total usage from 2002 to 2010 was over 113 billion doses in 15 countries, with China leading the total vaccine usage (>103 billion doses; 90.99%; Figs. 4, 5). This is followed by 5 billion doses in Egypt, 2.6 billion in Indonesia, and 1.6 billion in Vietnam, which account for 4.65%,

![Fig. 3. Summary of the doses of vaccine used in poultry for HPAI by year from 2002 to 2010.](image)

![Fig. 4. Summary of H5 vaccine doses used in poultry by the 15 countries vaccinating poultry against HPAI from 2002 to 2010.](image)
2.32%, and 1.43% of vaccine used against HPAI, respectively. Inactivated AI vaccines have accounted for 95.5%, and live recombinant virus vaccines have accounted for 4.5% of vaccine used. The latter was primarily recombinant Newcastle disease vectored vaccine with H5 influenza gene insert. These 113 billion doses were used in an at-risk national poultry population of 131 billion (41.9% coverage rate), compared to global poultry production of 520 billion (10.9% coverage rate). However, this high vaccine usage was associated with the very high poultry production in China, compared to a much lower production in Egypt, Indonesia, and Vietnam, and the even smaller usage in the other 11 countries/regions (Fig. 6). However, the usage rates varied in individual countries (Fig. 7), with a high of 86.2% for Hong Kong for all years, but when fully implemented in 2004, the program was 100% in Hong Kong, the only location to achieve a level of effective population immunity. In other countries, the vaccination programs reached a lower percentage of the poultry population because of the difficult logistics of implementing vaccination in sector 3 and 4 poultry. In addition, estimates of sector 3 and 4 poultry may be too low. For example, Egypt had a calculated 69.9% coverage rate based on official OIE production numbers, but with estimates from the Egyptian Ministry of Agriculture for a greater poultry population in sector 3 and 4 production systems, the vaccination coverage dropped to between 27.8% and 48.6% (29). The coverage rate for poultry in China, Mongolia, and Vietnam was approximately 50% (Fig. 7), but with the other 10 countries, coverage was less than 15%.

The type of poultry covered varied with vaccination program in each country. For 2004–09, Egypt concentrated most heavily on meat and breeder chickens (78.2% of 1.9 billion birds) and layers (31.6% of 91 million hens), and had much lower coverage in turkeys (10.4% of 8.1 million birds), ducks (15% of 60 million birds), and geese (1.4% of 40 million birds; Fig. 8). In contrast, Vietnam’s program obtained a higher vaccination rate in meat and breeder ducks (90% of 322 million population) and lower vaccination rate in meat and breeder chickens (50% of 1.3 billion population). Finally, Pakistan concentrated on higher vaccination rates among long-lived broiler and layer breeders (25.8% of 54 million population) and layers (2.8% of 344 million population), but did not vaccinate short-lived meat chickens (0% of 2.7 billion population). Usage of vaccine for control of H5/H7 LPNAI accounted for <10.1 billion doses, which corresponds to 8.1% of H5/H7 vaccine as compared to HPAI vaccine usage.

**Detailed intracountry application of vaccination in a HPAI control program.** Countries with highly functional, coordinated, adequately funded national, provincial, and local veterinary services had the greatest success with implementing and monitoring HPAI vaccination programs. These countries generally had predeveloped logistic plans for vaccination and had exercised vaccination plans as table-top or field exercises. Vaccines were available commercially or from a vaccine bank within the country, which indicated the vaccines had completed the licensing and registration process or the country had an emergency authority to use the vaccines. Generally, stockpiles of vaccine were available in the country through either existing manufacturing capacity or importation from countries that manufactured such vaccines. The time period when the vaccination program was initiated had an impact on success, such that shorter times between diagnosis of the index case and vaccination implementation impacted time to eradication. For vaccination to be effective, there must be population immunity within the control zone or compartment. This was easier to achieve with implementation of vaccination in industrial production sectors 1 and 2 than in semicommercial and village sectors 3 and 4 of least-developed and developing/transition countries. To be effective, population immunity must be a minimum of 60%, but optimal immunity requires >80% immunity in the susceptible at-risk poultry population. Single vaccination has been attempted for achieving protection in meat chickens, but such programs have not been effective in producing immunity in the field (22), and experimental studies have also questioned the utility of single-dose vaccine except under very defined conditions (10). To
achieve high population immunity economic incentives are required for farmers to vaccinate, and such vaccination must control a real disease and not a theoretical disease. For example, it has been difficult to convince farmers in least-developed and developing/transitional countries to vaccinate for the good of public health or to prevent a “pandemic” such as in domestic ducks, which have minimal disease to no disease in the field when infected with H5N1 HPAI virus. Vaccination compliance has dropped in Vietnam for sector 3 duck farms because the farmers do not see the benefit in livelihood and food security terms. The major reason for vaccine and vaccination “failure” in the field has been the inability to achieve population immunity in 80% of the susceptible population as the result of low vaccine coverage.
administration or coverage rate. In Egypt, for sectors 3 and 4, only 36% of the poultry are vaccinated, but in commercial sectors 1 and 2, the vaccination coverage is 50%–60% (22).

Recently, sporadic failures of vaccines and vaccination have been the result of continued usage of antigenically inappropriate vaccine seed strain after H5N1 HPAI viruses had circulated in the field for multiple years and antigenically drifted away from vaccine seed strains. This necessitates conducting ongoing surveillance of field strains and conducting challenge studies on a biannual basis using epidemiologically relevant field strains. This may require use of more than one seed strain or bivalent vaccines in countries with long-term vaccine use.

Field viruses have appeared in Egypt, China, Vietnam, Hong Kong, and Indonesia that are resistant to H5 vaccine seed strains, but not against H7 vaccine seed strains used in Pakistan (1,28). In Egypt, which has vaccinated poultry since early 2006, several field viruses have been identified that are resistant to classic seed strains Mexico/94 and RE-1 vaccine seed strains (2,7,14,28). China has also experienced reduced effectiveness of H5 seed strains, necessitating changes of vaccine seed strains as resistance occurred in the field. They have used various vaccine seed strains since 2004: A/Turkey/England/1973 (H5N2) LPNAI virus from 2004 to 2006; RE-1, a reverse genetic (rg) A/goose/Guangdong/1/1996 (H5N1), clade 0 lineage virus produced from 2004 to 2008; RE-4, an rgA/chicken/Shanxi/2006 (H5N1), clade 7 lineage virus produced for 2006–07; RE-5, a rgA/duck/Anhui/1/2006 (H5N1), clade 2.3.4 lineage virus produced from 2008; and RE-6, a rgA/duck/Guangdong/S1322/2010 (H5N1), clade 2.3.2.1 lineage virus with production beginning in 2012. In 2011, Vietnam identified several 2.3.2.1 strains resistant to immunity from RE-1 and RE-5 vaccines, and they proposed usage of a new RE-6 starting in 2012. Hong Kong experienced an H5N1 HPAI outbreak in a well-vaccinated flock during 2007. Historically, the classic H5 vaccines are antigenically similar, but H5N1 strains were isolated from flocks with "vaccine breaks" that overcame protection from Mexico/94, RE-1, and other H5 vaccine seed strains. H5 vaccine-resistant strains have not been reported from Pakistan, Russia, or the other countries that have used a more targeted vaccination program (29). Additional details of HPAI vaccination programs are presented elsewhere (29).

Vaccination protocols should be developed and tailored to fit the poultry species and type of bird, the production sector, and the immune status of the population. Movement controls on poultry populations are necessary to prevent dispersion of infected poultry to live poultry markets from any production sector, i.e., sectors 1, 2, 3, and 4.

**Future Directions in AI vaccines and vaccination.** Over the next 5 yr, specific changes will be needed to further improve vaccines and vaccination of poultry in controlling HPAI:

1) age- and species-specific targeted vaccination based on surveillance, and applied to both clinically affected and asymptptomatically infected species instead of attempts to apply vaccines through timed campaigns in all poultry within a country;

2) improved vaccines that can be applied by mass application methods such as aerosol, in ovo, feed, etc., and improvement of application methods for broader population coverage;

3) specific protocols to achieve a two-vaccine-dose regime at an early age, such as a priming vaccination at 1–10 days of age and a boost vaccination between 10 and 30 days of age;

4) Marek's disease herpesvirus vectored vaccine with H5 gene insert for single-dose protection for short-lived broilers, or priming with other recombinant vaccines (recombinant fowlpox virus or Newcastle disease vector with H5 gene insert) and boost with inactivated H5 AI vaccine.
5) recombinant vaccine for ducks and geese, such as duck virus enteritis (DVE) vaccine virus with AI HA gene that will protect from an economic disease (i.e., DVE) but also reduce infection by H5N1 HPAI virus; and
6) development of more realistic AI vaccine exit strategies based on risk models in current and future production systems, and not based on imposed time lines without scientific merit.

SUMMARY

Countries with high poultry density that are least economically developed have had the most difficulty in controlling/eradicating HPAI, emphasizing need to improve biosecurity and other parts of HPAI control programs. An effective HPAI control program requires good governance, transparency, competent veterinary services, and economic support. The primary strategy for HPAI and H5/H7 LPAI control will continue to be immediate eradication by a four-component strategy: education, biosecurity, rapid diagnostics and surveillance, and elimination of infected poultry. Vaccination can be a second tier component or “tool” when immediate eradication is not feasible, to maintain livelihoods and food security, and to control clinical disease until a primary strategy can be developed and implemented to achieve eradication.

ADDENDUM

After submission of the manuscript, an outbreak of H7N3 HPAI began in layer chickens in Mexico during June 2012. A stamping-out program has been initiated and vaccination of layers in the outbreak area has begun. This increases the number of HPAI epizootics since 1959 to 31.

REFERENCES


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