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Short communication

Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009–2010 and comparison with previous estimates and global action plan targets

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ABSTRACT

Immunization against influenza is considered among the most important interventions in reducing the public health impact of seasonal epidemic and pandemic influenza infections. However, there are marked differences across countries with regards to production, supply and access to influenza vaccines. A global action plan (GAP) to increase supply of pandemic influenza vaccine was developed by the World Health Organization in May 2006 to reduce the anticipated gap between potential vaccine demand and supply during an influenza pandemic. To quantify the increase in global influenza vaccine production capacity and actual production in response to the influenza A(H1N1) 2009 pandemic, 3 years after the development of the GAP, the WHO conducted a survey of vaccine producers from December 2009 through February 2010, and compared the results of this survey with results from surveys conducted in 2006–2007 and May 2009.

1. Introduction

Vaccination is recognized as one of the most effective tools for mitigating the impact of an influenza pandemic [1]. However, the effectiveness of a vaccination response depends upon a timely and sufficient supply of vaccine. The WHO organized a meeting in Geneva, Switzerland, in May 2006 to develop a global action plan with a goal of increasing influenza vaccine production and surge capacity during an influenza pandemic. The action plan developed from this gathering sought, in the short term, to enable production of enough vaccine to immunize two billion people within 6 months after a pandemic virus vaccine candidate becomes available [2]. The medium- and long-term objective was to enable the production of enough vaccine to immunize the world's population (6.7 billion people). This report summarizes global influenza vaccine production more than 3 years after the development of the global action plan in the context of the ongoing influenza A(H1N1) pandemic.

2. Methodology

Vaccine production data was collected via survey conducted by the WHO from December 2009 through February 2010. The questionnaire, developed in Excel® with Visual Basic Userform technology, was sent electronically to 33 current or potential influenza vaccine manufacturers with expected influenza vaccine production capacity by the second quarter of 2010.[1] An additional four manufacturers/facilities were not expecting to commence influenza vaccine production by 1 June 2010 and were not surveyed. The questionnaire requested each manufacturer's production (in millions of doses) of 2009–2010 trivalent seasonal Northern Hemisphere vaccine as of 1 December 2009 and plans for 2010 trivalent seasonal Southern Hemisphere vaccine production. The question-

[1] ADImmune Corporation; Baxter; Berna-Crucell; Bharat Biotech; Biken; Changchun Changsheng Life Sciences Limited; Chemo-Sero-Therapeutic Research Institute; Bio Farma; Cantacuzino Institute; CSL; Dalian Aleph Biomedical Co., Ltd; Denka Seiken; GlaxoSmithKline Biologicals; GPO Thailand; Green Cross Corporation; Henan Hualan Biological Engineering Inc.; Institute of Virology, Vaccines and Sera Torlak; IVAC; Kitasato; MedImmune; Microgen; Novartis Vaccines and Diagnostics; Omnivest; Panacea Biotec; Sanofi Pasteur; Serum Institute of India; Shenzhen Neptunus Bioengineering Co.; Sinopharm; Sinovac Biotech; Solvay Pharmaceuticals; Vabiotech; Zhejiang Tianyuan Bio-Pharmaceutical Co., Ltd; Zydus Cadila.

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Table 1
Actual and forecasted seasonal and pandemic influenza vaccine production 2009–2010.

Vaccine	Doses (millions)		
	Forecasted (June 2009) [4]	Forecasted (January 2010)	Actual production
Trivalent Northern Hemisphere seasonal (2009–2010)	493	–	500
Trivalent Southern Hemisphere seasonal (2010)	112[a]	73[b]	–
Monovalent H1N1 produced by 1 December 2009	2459		534
Inactivated[c]	–	–	511
Adjuvanted (various adjuvants)	–	–	169
Non-adjuvanted	–	–	342
Live attenuated	–	–	23
Monovalent H1N1 to be produced by 1 March 2010	3689	1303	–
Monovalent H1N1 to be produced by 1 June 2010	4918	1367	–

[a] 2009 season.
[b] 2010 season.
[c] Includes whole virion, split virion, sub-unit, and recombinant protein formulations.

naire also requested data on actual production (in millions of doses) of monovalent influenza A(H1N1) pandemic vaccine by formulation [inactivated or live attenuated, non-adjuvanted or adjuvanted (with adjuvant type), and antigen content per dose] as of 1 December 2009 and forecasted production of any formulation by 1 March 2010 and 1 June 2010.

3. Results

All 33 manufacturers (representing 37 production facilities) responded to the survey. Thirty-four facilities reported actual influenza vaccine production or intent to produce by 1 June 2010.

3.1. Seasonal influenza vaccine actual and forecasted production

The reported number of doses of Northern Hemisphere trivalent influenza vaccine produced for the 2009–2010 seasonal epidemic was 500 million, and the anticipated number of doses of Southern Hemisphere trivalent influenza vaccine to be produced for the 2010 epidemic season was 73 million (Table 1).

3.2. Pandemic H1N1 vaccine actual and forecasted production

The number of doses of monovalent pandemic H1N1 vaccine produced by 1 December 2009 was 534 million, with the vast majority (96%) of these doses being the inactivated formulation. Of the inactivated vaccines, two-thirds of the doses produced were non-adjuvanted. The number of doses of monovalent pandemic H1N1 vaccine of any formulation forecasted to be produced by 1 March 2010 and 1 June 2010 was 1303 million doses and 1367 million doses, respectively.

3.3. Number and global distribution of influenza vaccine production facilities

There are 41 current ($n = 34$) and potential future ($n = 7$) influenza vaccine production facilities distributed globally in 25 countries, including 9 countries newly able to manufacture influenza vaccine or with credible plans to develop such an activity (Fig. 1). The majority of these 41 facilities are located in the WHO geographic regions of the Western Pacific (WPR) and Europe (EUR), with 16 (39%) and 12 (26%) manufacturing sites, respectively (Table 2). Of the 34 facilities with actual or planned influenza vaccine production by 1 June 2010, 15 (44%) were in the WPR and 12 (35%) were in the EUR regions. One manufacturer in the South East Asia region (SEAR) produced seasonal vaccine in 2009 and other manufacturers from this region anticipate pandemic H1N1 vaccine production by June 2010. Production is expected to commence in the next 5 years from seven manufacturers located in the Americas region (AMR, $n = 2$), the Eastern Mediterranean region (EMR, $n = 2$), SEAR ($n = 2$), and WPR ($n = 1$). There are no manufacturers currently, or under development, in sub-Saharan Africa (AFR).

3.4. Influenza vaccine production by WHO region

For the 2009–2010 Northern hemisphere epidemic, seasonal trivalent vaccine was produced predominantly in three of the six WHO regions. Of the 573 million doses of trivalent vaccine produced, 49% (283 million doses), 26% (151 million doses), and 23% (133 million doses) were produced in EUR, AMR, and WPR, respectively. Similarly, of the 1367 million doses of monovalent pandemic H1N1 vaccine forecasted to be produced by 1 June 2010, 46% (636 million doses), 30% (410 million doses), and 21% (293 million doses) are projected to originate from EUR, AMR, and WPR.

4. Discussion

The influenza A(H1N1) 2009 pandemic provided an opportunity to monitor actual global influenza vaccine production capacity and the progress made in production capacity since the development of the global action plan (GAP) in 2006. In 2006, the global estimated annual production capacity of trivalent seasonal influenza vaccine was 350 million doses [3], with production mostly concentrated in nine industrialized countries. By 2010, production capacity is projected to have sharply increased to over 800 million doses [4], mainly due to substantial investment by multinational manufacturers in new and enlarged production plants. Importantly, production capacity is currently available or is being established in 25 countries, including developing countries as part of the WHO technology transfer program. This will serve not only to increase global production, but will also enable more equitable access to vaccine in the event of future pandemics. Despite this progress, adequate production capacity is still lacking in some regions of the world, particularly in sub-Saharan Africa and Central Asia. And, despite the emergence of new influenza vaccine manufacturers globally, more than 80% of seasonal influenza vaccine doses produced in 2009–2010 will have originated from the seven large manufacturers that are located in the USA, Canada, Australia, western Europe, Russia, China, and Japan [4]. Moreover, a large proportion of expected pandemic vaccine production was already reserved before the onset of the pandemic by high-income country governments through advanced-purchase agreements, or was purchased by these governments very early in the pandemic [4]. As a result, there was no pandemic H1N1 vaccine available in most developing countries before January 2010, more than 8 months after the pandemic was declared by the WHO.

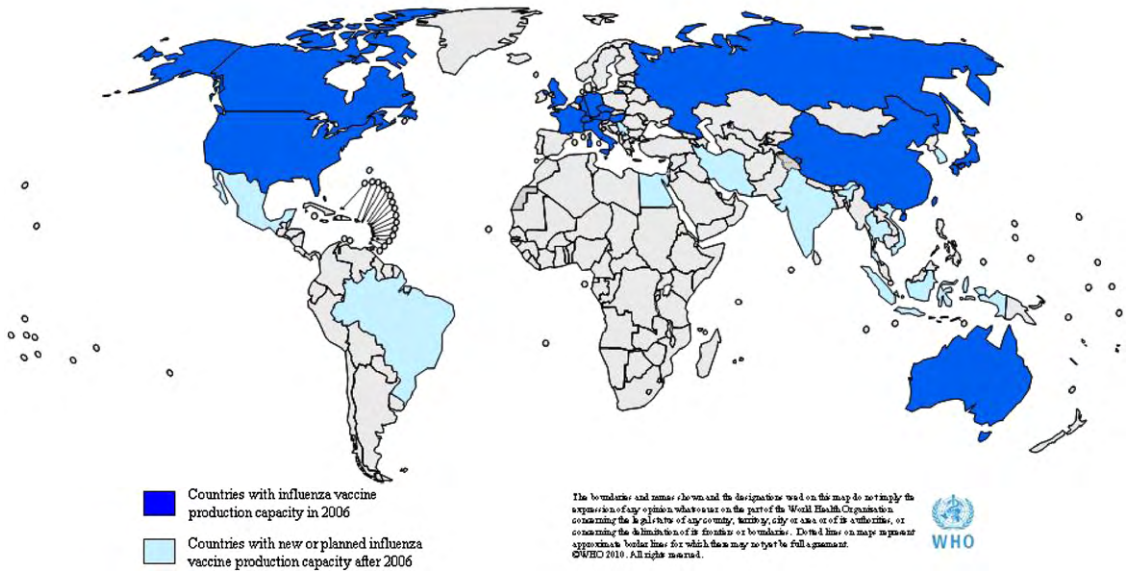

Fig. 1. Countries with influenza vaccine production capacity in 2006 and 2010.

Table 2
Influenza vaccine production by WHO Region in 2009–2010.

WHO region	Number of countries with production facilities	Number of production facilities	Projected seasonal vaccine production[a] (doses in millions)	Projected pandemic H1N1 vaccine production[b] (doses in millions)
AFR	0	0	0	0
AMR	4[c]	5	151	410
EMR	2[d]	2	0	0
EUR	11	12	283	636
SEAR	3	6	6	28
WPR	5	16	133	293
Total	25	41	573	1367

[a] Including actual Northern Hemisphere produced in 2009 and forecasted Southern Hemisphere production in 2010.
[b] Forecasted to be produced by 1 June 2010.
[c] No production anticipated from Brazil and Mexico by June 2010.
[d] No production anticipated by June 2010.

The first commercially available pandemic influenza vaccines were registered for use in September 2009, 5 months after the identification of the pandemic A(H1N1) 2009 virus (Fig. 2). The time from identification of the novel virus to the availability of the first candidate vaccine was relatively short (approximately 6 weeks), and vaccine production progressed rapidly. Although accelerated licensing processes were considered in many countries, clinical trial results were requested by regulatory agencies in order to confirm safety of the products, to assess appropriate antigen content in pandemic vaccines, and to confirm the number of doses required to induce protective immunity in vaccinees. Given the public concern in many countries possibly created or exacerbated by the improper

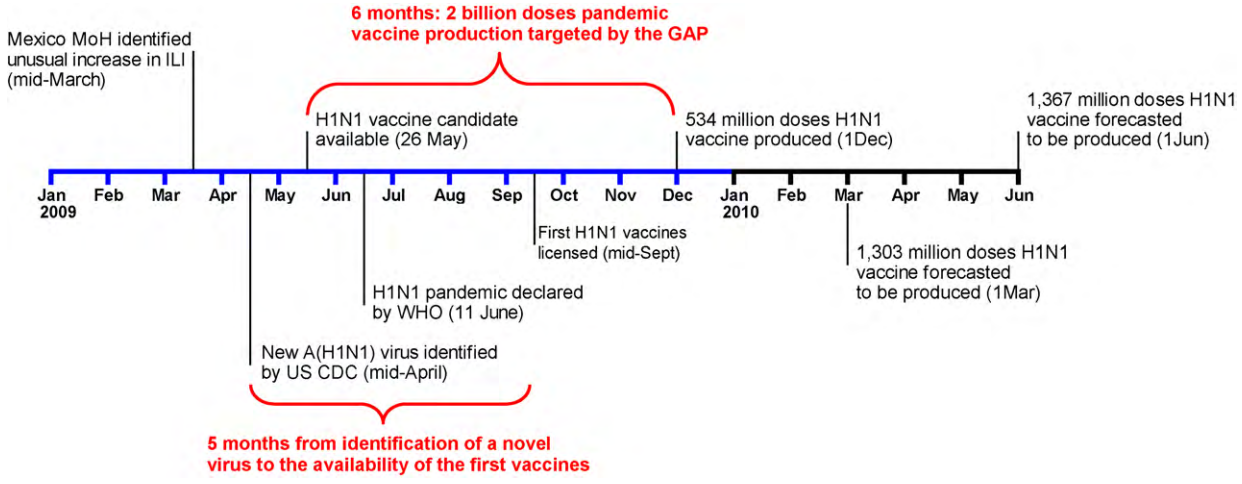

Fig. 2. Timeline for identification of the novel influenza H1N1 virus to production of vaccine.

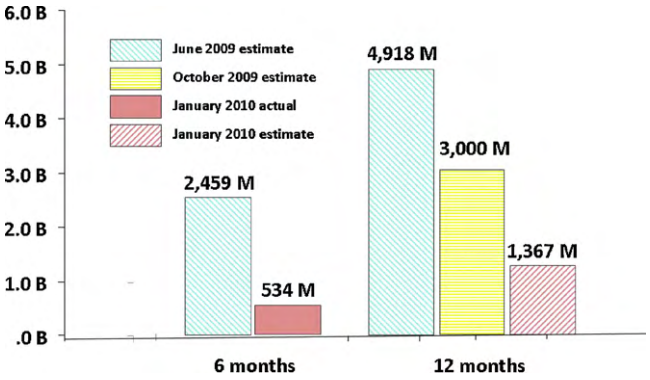

Fig. 3. Global pandemic (H1N1) 2009/2010 vaccine supply: estimated versus actual production (as of January 2010).

characterization by the media of the H1N1 vaccines as being "novel" or "untested" [5], it is clear in retrospect that thorough regulatory oversight is essential prior to authorization for use. Finally, in spite of considerable efforts deployed by all stakeholders, the number of pandemic doses available for use in vaccination programs globally was well below the WHO's GAP targets. While the short-term goal set by the GAP was the availability of enough vaccine to immunize two billion people with one dose within 6 months after the transfer of the vaccine prototype strain to industry (i.e., December 2009), the actual global production by 1 December 2009 was only 534 million doses of monovalent vaccine.

The forecasted production of pandemic vaccine 12 months after the availability of the vaccine virus (i.e., June 2010) is approximately 1.37 billion doses, which is only 28% of the annual global production capacity of 4.9 billion doses estimated from the WHO survey conducted in May 2009 [4, Fig. 3]. The reasons for this low pandemic vaccine output, other than actual capacity, include lower than expected vaccine virus yields (the H1N1 vaccine to seasonal vaccine yield was only 1:3 rather than 1:1 as assumed in the May 2009 survey), the inability of manufacturers to use their most dose-sparing formulation, the reluctance of certain regulatory authorities to register adjuvanted low-antigen dose vaccine formulations, shrinking vaccine demand due to delayed vaccine availability in some parts of the world and in the face of a pandemic of moderate severity, and the stopping of pandemic vaccine production by some producers in late 2009 and by almost all manufacturers in early 2010 to switch to Southern and Northern Hemisphere seasonal vaccine production, respectively.

Despite considerable progress made to narrow gaps identified in 2006 between production capacity and actual production of influenza vaccine, marked challenges remain to achieve the goal of producing enough vaccine to cover the world's population. More than 3 years after the development of the GAP, progress is still needed to promote seasonal vaccine use to increase production capacity through market forces and to ensure sustainability of new capacity, to establish more vaccine manufacturing capacity in developing countries, and continue research and development for new vaccines and technologies to support rapid production of pandemic vaccines once a pandemic has been identified. Further progress will require political commitment, scientific innovation, significant funding, close international cooperation, and partnerships among WHO, member states, donor institutions, vaccine manufacturers, and other stakeholders.

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References

[1] Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. Nature 2006;442(7101):448–52.
[2] World Health Organization. Global pandemic influenza action plan to increase vaccine supply. Department of Immunization, Vaccines and Biologicals; 2006.
[3] Kieny MP, Costa A, Hombach J, Carrasco P, Pervikov Y, Salisbury D, et al. A global pandemic influenza vaccine plan. Vaccine 2006;24(40–41):6367–70.
[4] Collin N, de Radigues X. Vaccine production capacity for seasonal and pandemic (H1N1) 2009 influenza. Vaccine 2009;27:5184–6.
[5] Rachiotis G, Mouchtouri VA, Kremastinou J, Gourgoulianis K, Hadjichristodoulou C. Low acceptance of vaccination against the 2009 pandemic influenza A(H1N1) among healthcare workers in Greece. Euro Surveill. 2010; 15(6):pii = 19486. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19486.