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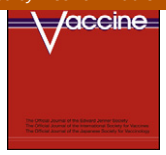

Global production capacity of seasonal influenza vaccine in 2011

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ABSTRACT

The effectiveness of vaccines to mitigate the impact of annual seasonal influenza epidemics and influenza pandemics has been well documented. However, the steady increase in global capacity to produce annual seasonal influenza vaccine has not been matched with increased demand, and thus actual vaccine production. Currently, without a significant increase in demand for seasonal influenza vaccine, global capacity will be far from able to meet even the essential needs for a monovalent vaccine in the event of a severe influenza pandemic. Global commitment to the development of influenza vaccine production capacity was renewed at a consultation leading to the Second Global Action Plan on Influenza Vaccines (GAP) in July 2011. To monitor progress on the GAP, the World Health Organization has carried out periodic surveys of influenza vaccine manufacturers. This latest survey compares current maximum global capacity and actual production of seasonal influenza vaccine in 2011 with data from surveys carried out in 2009 and 2010; analyses global influenza production capacity in the context of sustainability; and discusses options to increase demand, based on strong evidence of public health benefit.

1. Introduction

The effectiveness of vaccines to mitigate annual seasonal influenza epidemics and the potentially devastating impact of influenza pandemics has been well documented. What is sometimes less recognized is the intrinsic link between production capacity for seasonal influenza vaccine – which tends to be aligned with demand by immunization programmes – and potential vaccine availability for pandemic influenza vaccination. Indeed, rapid production of a pandemic influenza vaccine in the billions of doses needed to meet expected demand currently depends entirely on global capacity to produce seasonal trivalent influenza vaccines.

The Global Action Plan on Influenza Vaccines (GAP), published in 2006, is a comprehensive strategy to reduce the global shortage of influenza vaccines for seasonal epidemics and severe pandemics in all countries through three main approaches: (1) increasing seasonal vaccine use; (2) increasing vaccine production capacity; and (3) research and development [1]. Since 2006, significant progress has been made: new and expanded facilities have been announced in both developed and developing countries; the amount of antigen required per dose is now lower due to new adjuvants; production yields have improved; and advances have been made with new technologies. Global commitment to the development of influenza vaccine production capacity was renewed at a consultation leading to the Second GAP in July 2011 [2]. To monitor progress on vaccine production capacity, the World Health Organization (WHO) has carried out periodic surveys of influenza vaccine manufacturers. The latest survey compares current maximum global capacity and actual production of seasonal influenza vaccine in 2011 with data from surveys carried out in 2009 and 2010 [3,4], analyses global influenza production capacity in the context of sustainability, and discusses options to increase demand, based on strong evidence of public health benefit.

2. Methodology

New information on global seasonal influenza vaccine production capacity was collected via a survey conducted by WHO from December 2011 to April 2012. The questionnaire, developed in Microsoft Excel®, was sent electronically to all known (28) vaccine manufacturers with established seasonal influenza vaccine production capacity in 2011.[1] The questionnaire requested each manufacturer to report both its estimated total production capac-

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ity and its actual production (in millions of doses) of 2011 trivalent seasonal Southern Hemisphere (SH) vaccine and/or 2011–2012 trivalent seasonal Northern Hemisphere (NH) vaccine by type of formulation [inactivated or live attenuated, non-adjuvanted or adjuvanted (with adjuvant type), and antigen content per dose]. Manufacturers with multiple production facilities were requested to report capacity and production data aggregated across the countries if the facilities were in the same WHO Region. Manufacturers were requested to disaggregate these data by WHO Region if their facilities were located in more than one WHO Region. Information on future vaccine production facilities was obtained through the GAP programme at WHO.

3. Results

Twenty-seven vaccine manufacturers (96%) responded to the survey. For the one manufacturer who did not respond, data provided in 2010 was used in the analysis, as no major change in the company had taken place between 2010 and 2011. The estimated global annual capacity for seasonal trivalent influenza vaccine production was 1420 million doses, with 75% of this capacity dedicated to NH vaccine production (Table 1). This represents an increase of 544 million doses (62%) over the previous estimates based on data from the 24 manufacturers with production capacity in 2009 [3].

3.1. Seasonal influenza vaccine production

In 2011, 25 manufacturers representing 34 production facilities produced 620 million doses of seasonal trivalent influenza vaccine, which was an increase of 47 million doses (8%) from the 2009 estimated production of 573 million doses [4]. Twenty-three (68%) facilities produced only NH vaccines and 11 (32%) produced both NH and SH vaccines. No facilities produced only SH vaccines. Three manufacturers reported capacity to produce influenza vaccines, but did not produce trivalent seasonal influenza vaccine in 2011.

Table 1
Capacity and actual production of seasonal trivalent influenza vaccine in 2009 and 2011.

Vaccine	Doses (millions)	
	2009	2011
Seasonal trivalent vaccine capacity	876	1420
Northern Hemisphere seasonal vaccine *capacity*		1069
Northern Hemisphere seasonal vaccine *production*	470[a], 500[b]	534[c]
Inactivated Northern Hemisphere vaccine produced for 2011/2012 season		506
15 μg antigen for each component (non-adjuvanted)		447
15 μg antigen for each component (adjuvanted)		30
7.5 μg antigen for each component (non-adjuvanted)		14
5 μg antigen for each component (adjuvanted)		14
Live attenuated Northern Hemisphere vaccine produced for 2011/2012 season		29
Southern Hemisphere seasonal vaccine *capacity*		352
Southern Hemisphere seasonal vaccine *production*	112[d], 73[e]	86[f]
Inactivated Southern Hemisphere vaccine produced for 2011/2012 season		86
15 μg antigen for each component (non-adjuvanted)		79
15 μg antigen for each component (adjuvanted)		7
Live attenuated Southern Hemisphere vaccine produced for 2011/2012 season		0

[a] 2008/2009 season.
[b] 2009/2010 season.
[c] 2011/2012 season.
[d] 2009 season.
[e] 2010 season.
[f] 2011 season.

3.2. Northern Hemisphere seasonal influenza vaccine estimated capacity and actual production

The estimated global annual capacity for NH seasonal trivalent influenza vaccine production in 2011 was 1069 million doses, while the reported number of doses actually produced for the 2011–2012 season was 534 million doses, i.e. only 50% of global capacity. Of actual NH vaccine production, the vast majority of doses (86%) were the inactivated non-adjuvanted formulation. The estimated annual production capacity in 2011 was a 22% increase over the 876 million doses estimated in 2009 [3], while actual NH production increased 7% in 2011 compared with the 2009 estimate [4].

3.3. Southern Hemisphere seasonal influenza vaccine estimated capacity and actual production

The reported global annual capacity for SH seasonal trivalent influenza vaccine production in 2011 was 352 million doses, while the reported number of doses actually produced for the 2011 season was 86 million doses, i.e. only 24% of global capacity. Only doses of the inactivated formulation were produced, 92% of which were non-adjuvanted. Actual SH production decreased 23% in 2011 compared with the 2009 estimate [3].

3.4. Current and future seasonal influenza vaccine production by WHO Region

In 2011 there were 21 countries with seasonal trivalent influenza vaccine production capacity (Table 2). Production capacity was estimated as 691 million doses (48%) in the WHO European Region (EUR), 378 million doses (27%) in the Region of the Americas (AMR), 324 million doses (23%) in the Western Pacific Region (WPR), and 28 million doses (2%) in the South-East Asia Region (SEAR) (Fig. 1). In terms of actual production, EUR produced nearly

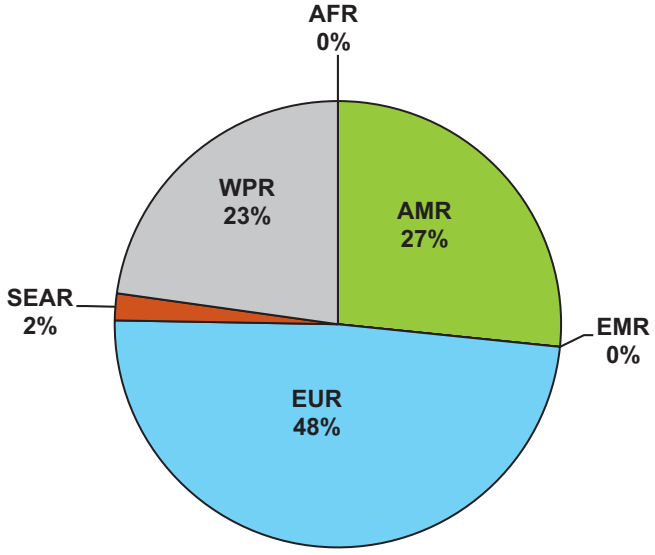

Fig. 1. Global production capacity of seasonal trivalent influenza vaccine in 2011 by WHO Region. AFR, WHO African Region: no trivalent seasonal vaccine production capacity in 2011. AMR, WHO Region of the Americas: trivalent seasonal vaccine production capacity in 2011 in Canada and the United States of America. EMR, WHO Eastern Mediterranean Region: no trivalent seasonal vaccine production capacity in 2011. EUR, WHO European Region: trivalent seasonal vaccine production capacity in 2011 in Austria, Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Romania, Russian Federation, Serbia, Switzerland and United Kingdom. SEAR, WHO South-East Asia Region: trivalent seasonal vaccine production capacity in 2011 in India and Indonesia. WPR, WHO Western Pacific Region: trivalent seasonal vaccine production capacity in 2011 in Australia, China, Japan and Republic of Korea.

Table 2
Seasonal trivalent influenza vaccine production by WHO Region in 2011.

WHO Region	Number of countries with production capacity in 2011	Additional countries with production capacity planned after 2011	Estimated production capacity of NH vaccine (doses in millions)	Actual production of NH vaccine 2011/2012 season (doses in millions)	Estimated production capacity of SH vaccine (doses in millions)	Actual production of SH vaccine 2011 season (doses in millions)
AFR	0	1	0	0	0	0
AMR	2	2	282	131	96	28
EMR	0	2	0	0	0	0
EUR	13	2	514	252	177	54
SEAR	2	1	9	0.044	19	0
WPR	4	1	264	151	60	4
Total	21	9	1069	534	352	86

NH, Northern Hemisphere; SH, Southern Hemisphere; AFR, WHO African Region: no trivalent seasonal vaccine production capacity in 2011; AMR, WHO Region of the Americas: trivalent seasonal vaccine production capacity in 2011 in Canada and the United States of America; EMR, WHO Eastern Mediterranean Region: no trivalent seasonal vaccine production capacity in 2011; EUR, WHO European Region: trivalent seasonal vaccine production capacity in 2011 in Austria, Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Romania, Russian Federation, Serbia, Switzerland and United Kingdom; SEAR, WHO South-East Asia Region: trivalent seasonal vaccine production capacity in 2011 in India and Indonesia; WPR, WHO Western Pacific Region: trivalent seasonal vaccine production capacity in 2011 in Australia, China, Japan and Republic of Korea.

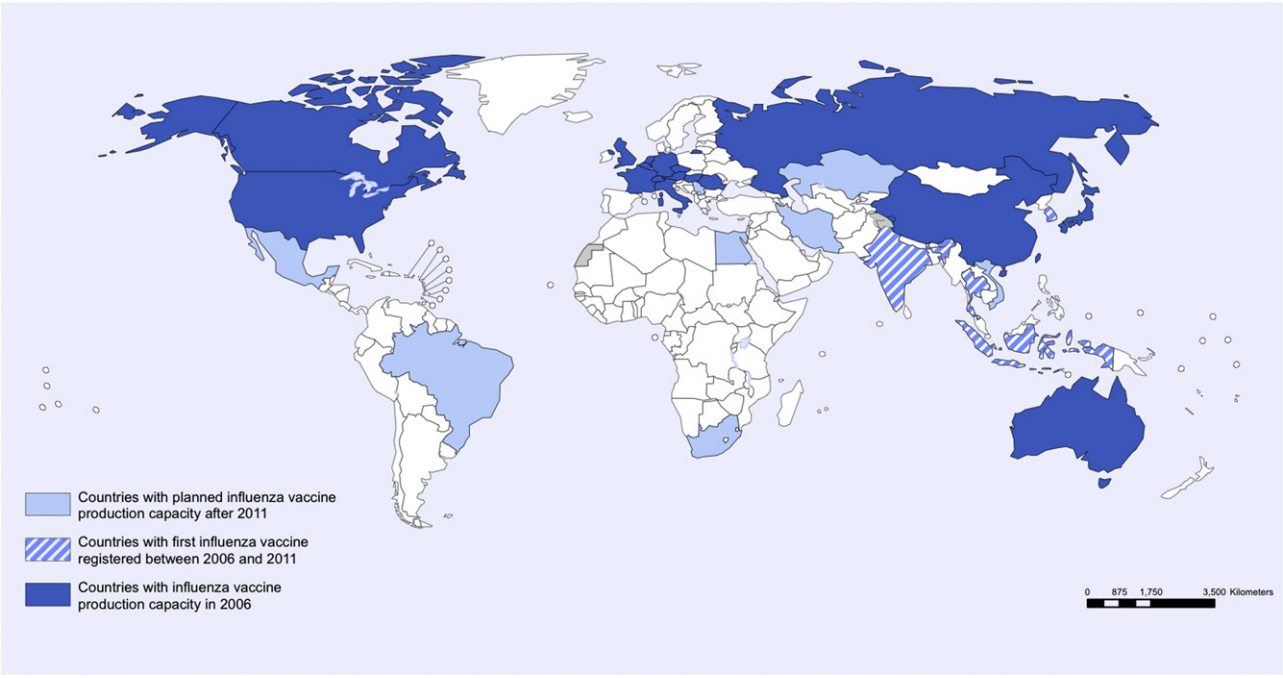

Fig. 2. Global influenza vaccine production capacity in 2006 and 2011 and production capacity planned after 2011.

50% of the global supply of NH vaccine followed by AMR, WPR and SEAR which produced 26%, 25% and <1% of global supply, respectively. For SH vaccine, nearly 62% of global supply was produced in EUR followed by 33% in AMR and 5% in WPR. No seasonal trivalent influenza vaccine was produced in 2011 in the WHO Regions of Africa (AFR) or the Eastern Mediterranean (EMR); however, capacity is currently being developed in countries in these two regions along with additional countries in AMR, EUR, SEAR and WPR (Fig. 2).

4. Discussion

This is the third survey undertaken as part of ongoing monitoring of the progress of WHO's Global Action Plan for influenza vaccines [1]. Since the start of the GAP, vaccine production capacity has not only grown in terms of the estimated number of doses that could be produced, but has also expanded geographically. In 2006 when the GAP was developed, only 17 countries produced seasonal influenza vaccine. By 2011, seasonal influenza vaccine was produced in 21 countries, and 8 further low- or middle-income countries (LMIC) plan production in the near future.

This potential increase in seasonal influenza production in LMIC can be attributed in part to the WHO Technology Transfer Initiative, launched in 2008 under the auspices of the GAP. To date, WHO has awarded grants to manufacturers in 14 countries (Brazil, China, Egypt, India, Indonesia, Islamic Republic of Iran, Kazakhstan, Mexico, Republic of Korea, Romania, Serbia, South Africa, Thailand and Viet Nam) to develop influenza vaccine manufacturing technology. Of these, manufacturers in four countries (India, Republic of Korea, Romania and Thailand) have licensed pandemic vaccines, two countries (Republic of Korea and Romania) have licensed trivalent seasonal vaccines on the market, and the remaining manufacturers have vaccines in various stages of development. Although this will lead to improved vaccine access in LMIC, the capacity of the new GAP-supported facilities will be largely limited to covering their essential needs and, at best, those of neighbouring countries, unless significant markets can be identified for the larger manufacturers. In addition, there remains a major imbalance in access for some geographic areas of the world, particularly in Africa and the Middle East.

Progress towards the GAP objective to increase global vaccine production capacity and simultaneously increase equitable

access to vaccine in LMIC has been impressive. However, using a simplified hypothesis that the production of one dose of seasonal trivalent vaccine is equivalent to three doses of monovalent pandemic vaccine, the estimated current annual production capacity for a pandemic vaccine would be 4260 million doses. This would hypothetically meet the GAP short-term goal of enabling production of enough vaccine to immunize two billion people with two doses of vaccine within six months, but is short of the medium- and long-term goals of enabling production of enough vaccine to immunize the world's population. In addition, this estimate is limited by several factors, including the assumption that the antigen yield will be similar for seasonal and pandemic vaccines.

Maintaining and continuing to increase global vaccine production capacity require concomitant increase in demand for seasonal vaccination. In comparison with the 2009 estimate of 876 million doses [3], the annual global capacity to produce trivalent seasonal influenza vaccine increased more than 1.6-fold or by 544 million doses by 2011; however, actual production has remained nearly the same at 613 million doses in 2009 [3,4] and 620 million doses in 2011, suggesting a lack of increase in demand for seasonal influenza vaccine during this period. Without uptake of seasonal influenza vaccine in national immunization programmes, based on local burden of disease and cost-effectiveness, manufacturers will be compelled to reduce their capacity in the future, and investment in the newer influenza vaccine facilities in developing countries may not bear its full potential. Therefore, the GAP is focusing increasingly on the objective to increase seasonal vaccine use through multiple activities, including assessment of disease burden, assessment of current and planned seasonal vaccine use and potential pandemic vaccine demand, strengthening national immunization advisory committees, and supporting immunization policy development.

One promising opportunity to accelerate progress in the uptake of seasonal influenza vaccine is collaboration of the GAP with the WHO Pandemic Influenza Preparedness (PIP) framework [5]. The mandate of the PIP framework is to ensure equity in influenza pandemic preparedness and response through a benefit-sharing approach. In addition to pre-arranged agreements with manufacturers to secure pandemic vaccine for procurement via WHO for developing countries, the GAP overall objectives will benefit from studies on disease burden, cost-effectiveness, and the evidence-based use of seasonal influenza vaccine and adjuvants. Such studies are fundamental to increase seasonal influenza uptake and to sustain global influenza vaccine production capacity.

With a view to updating the 2005 WHO recommendations on the use of seasonal influenza vaccine, the Strategic Group of Experts on immunization (SAGE) commissioned an evidence-based review of disease burden and vaccine performance and safety in all age and at-risk groups. Data were particularly sought from within LMIC. Based on the results of the analysis, SAGE recommended that pregnant women should be the first target group as they are at substantial risk of severe disease [6]. The potential benefits of vaccinating health-care workers, and young children for herd effects and potentially improving childhood survival, were also acknowledged. Other priority groups considered were the elderly, indigenous populations and persons with high-risk conditions. The successful implementation of these recommendations will require educational programmes and social messaging, along with year-round availability of safe and efficacious vaccines. However, the ultimate impetus for countries to promote seasonal influenza vaccination will depend on local epidemiology, capacity and cost-effectiveness. GAP will therefore devote enhanced attention to these avenues in order to translate evidence into increased seasonal influenza vaccine uptake.

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