GLOBAL PROGRESS REPORT

Global Action Plan for Influenza Vaccines

2006–2016

World Health Organization

GAP

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Acronyms and abbreviations

AFRO	WHO Regional Office for Africa
AG	Advisory Group
AMRO	WHO Regional Office for the Americas
BARDA	Biomedical Advanced Research and Development Authority
EMRO	WHO Regional Office for the Eastern Mediterranean
EQAP	External Quality Assessment Project
EURO	WHO Regional Office for Europe
GAP	Global Action Plan for Influenza Vaccines
GBT	Global Benchmarking Tool
GISRS	Global Influenza Surveillance and Response System
HHS	USA Department of Health and Human Services
HIC	high-income countries
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
ILI	influenza-like illness
JRF	WHO–UNICEF Joint Reporting Form
LAIV	live attenuated influenza vaccine
LMIC	low- and middle-income countries
NIC	national influenza centre
NRA	national regulatory authority
PIP	Pandemic Influenza Preparedness (Framework)
RT-PCR	reverse transcriptase polymerase chain reaction
SAGE	Strategic Advisory Group of Experts on Immunization
SARI	severe acute respiratory infection
SEARO	WHO Regional Office for South-East Asia
SMTA2s	standard material transfer agreements
UNICEF	United Nations Children's Fund
USA	United States of America
VLP	virus-like particle
WPRO	WHO Regional Office for the Western Pacific

Overview

Stemming from World Health Assembly resolution 56.19 *(1)*, the World Health Organization's (WHO's) Global Action Plan for Influenza Vaccines (GAP) was a response to the predicted global shortage of influenza vaccine and inequitable access in the event of a pandemic.

The GAP covered the decade from 2006 to 2016; its overall goal was to expand global production capacity to produce sufficient vaccine to immunize 70%[1] of the global population with two doses of vaccine (equal to about 10 billion doses) within 6 months of the vaccine virus strain being transferred to vaccine manufacturers.[2] The GAP spurred actions across the influenza vaccine sector (including vaccine producers), international public health agencies and research organizations. An Advisory Group (AG) guided the progress of the GAP.

The three objectives that guided the work during the decade of the GAP were as follows:

Objective 1

To increase evidence-based seasonal influenza vaccine use, ensuring that all countries[3] have a policy in place, and are on track in its implementation, to vaccinate at least one at-risk population group.

Actions

- **increasing data collection** regarding the burden of influenza, vaccine efficacy and cost–effectiveness at national and regional levels;
- **developing and strengthening existing disease and virologic surveillance systems**;
- **developing targeted regional and national seasonal influenza vaccination plans** and campaigns; and
- **supporting communication and awareness of the broader benefits and implications of influenza vaccinations**, with an emphasis on the target groups recommended by SAGE, including pregnant women, health care workers, the elderly, children and people with chronic conditions.

1 The 70% goal was included during the revision of the GAP in 2011.
2 The total global population expanded during the GAP decade; hence, the global population estimate used in this report was 7.303 billion people in 2015.
3 For this report, the word "country" has the meaning of "WHO Member State".

Objective 2

To increase pandemic vaccine production capacity and corresponding national regulatory competencies (to meet WHO criteria) towards the target of producing enough doses to vaccinate at least 70% of the world's population in the event of a pandemic, and to spread production across the world to facilitate rapid and equitable access.

Actions

- **establishing and expanding sustainable influenza vaccine production** in low- and middle-income countries (LMIC);
- **developing surge production capacity**; and
- **strengthening the capacity of national regulatory authorities** to license imported or locally manufactured influenza vaccines.

Objective 3

To develop more effective influenza vaccines with the aim to license, or to have in advanced clinical development, new influenza vaccines that are higher yielding, and/or faster to produce, and/or broader in protection and/or of a longer duration of protection when compared with the current licensed vaccines.

Actions

- **promoting research and development in new vaccine concepts** (e.g. universal vaccines), correlates of protection, prototype pandemic seed strains and other new technologies that shorten the influenza vaccine production timeline (e.g. potency testing and sterility testing); and
- **facilitating the exchange of information** between researchers working on new influenza vaccines.

Following a request from the GAP AG, a monitoring and evaluation framework was developed to track progress in achieving the targets set in 2006 (and revised in 2011) for the three GAP pillars. This framework was developed in consultation with the Global Influenza Programme; the Pandemic Influenza Preparedness (PIP) Framework Secretariat; the Immunization, Vaccines and Biologicals Department; and other internal and external stakeholders. WHO prepared a draft report of the framework in March 2013 to test the availability of baseline data, feasibility of data collection and calculation, and usefulness for monitoring changes and developments. Following the GAP AG meeting on 19 March 2013, the indicators were refined. The *Global Action Plan for Influenza Vaccines global progress report for January 2006–September 2013* was published in March 2014 ***(2)***.

As a time-bound programme, the GAP formally concluded in 2016. This report aims to provide a comprehensive overview of global progress made throughout the GAP decade. There are some discrepancies with the 2013 progress report because several indicators evolved or data were updated owing to new data becoming available or improved data collection systems, or to reflect new mechanisms or processes. Most notably, indicator 1.7, "percentage of targeted at-risk populations vaccinated" in the 2013 GAP progress report, was removed because of a lack of reliable data, and indicator 2.2, "number of LMIC vaccine manufacturers with annual supply agreements in place for seasonal influenza vaccines", was replaced by "cumulative number of LMIC that have conducted a sustainable local production or procurement of influenza vaccine assessment". In addition, to reflect the available data, indicator 3.1 was revised from "number of novel products under development" to "number of influenza vaccines under development". Thus, this report provides a comprehensive overview of the global progress made throughout the decade of the GAP, and stands as a corrected version of the 2013 progress report.

This GAP global progress report 2006–2016 reviews 14 progress indicators – seven corresponding to Objective 1, four corresponding to Objective 2 and three corresponding to Objective 3 – and includes progress summaries for each objective. It also assesses the GAP target indicator (the overarching measure of the effectiveness of the GAP), to support the development of influenza vaccine production capacity to vaccinate 70% of the world's population in the event of a pandemic.

Key highlights

Key highlights of the GAP decade are as follows:

- In 2006, **74 (38%) Member States** reported having a seasonal influenza vaccination policy in place. By 2014, this number had increased to 115 (59%) Member States ***(3)***.
- Over the GAP decade, the number of Member States with a WHO Global Influenza Surveillance and Response System (GISRS) national influenza centre (NIC) increased from 79 (41%) in 2006 to **113 (58%) in 2016** ***(4)***.
- The estimated global annual seasonal vaccine production capacity increased from 500 million doses in 2006 to **1.46 billion doses in 2015** ***(5)***.
- The potential global pandemic vaccine production capacity, over a 12-month period, was **6.37 billion doses in 2015**, a fourfold increase from 1.5 billion doses in 2006. The increase can be attributed to the rise from eight to 15 manufacturers producing vaccine, and the use of antigen-sparing or high-yield technologies ***(5)***.
- The number of developing countries with licensed pandemic influenza vaccines went from **zero in 2006 to four countries in 2016**.
- In collaboration with partners, WHO provided **technology transfer to 14 LMIC to support local influenza vaccine production**. Six countries had licensed eight pandemic influenza vaccines (two are WHO prequalified) and three seasonal vaccines (one is WHO prequalified) by 2016. Additional products are expected to be licensed before 2020 ***(6)***.
- Regulatory capacity continued to increase. Over the GAP decade, of the 14 countries that received support under the GAP, the number successfully operating a mature national regulatory authority (NRA) increased from four (29%) to **10 (71%)**.
- In 2006, **30 influenza vaccine clinical trials** were registered, compared with 322 clinical trials registered in 2016 ***(7)***.

PROGRESS UNDER

1 Objective 1: Increase use of seasonal influenza vaccines

TARGET: All countries to have a policy in place and implemented to vaccinate on an annual basis at least one group of their at-risk populations (as defined by either their national guidelines or by World Health Assembly resolution WHA56.19) by 2016.

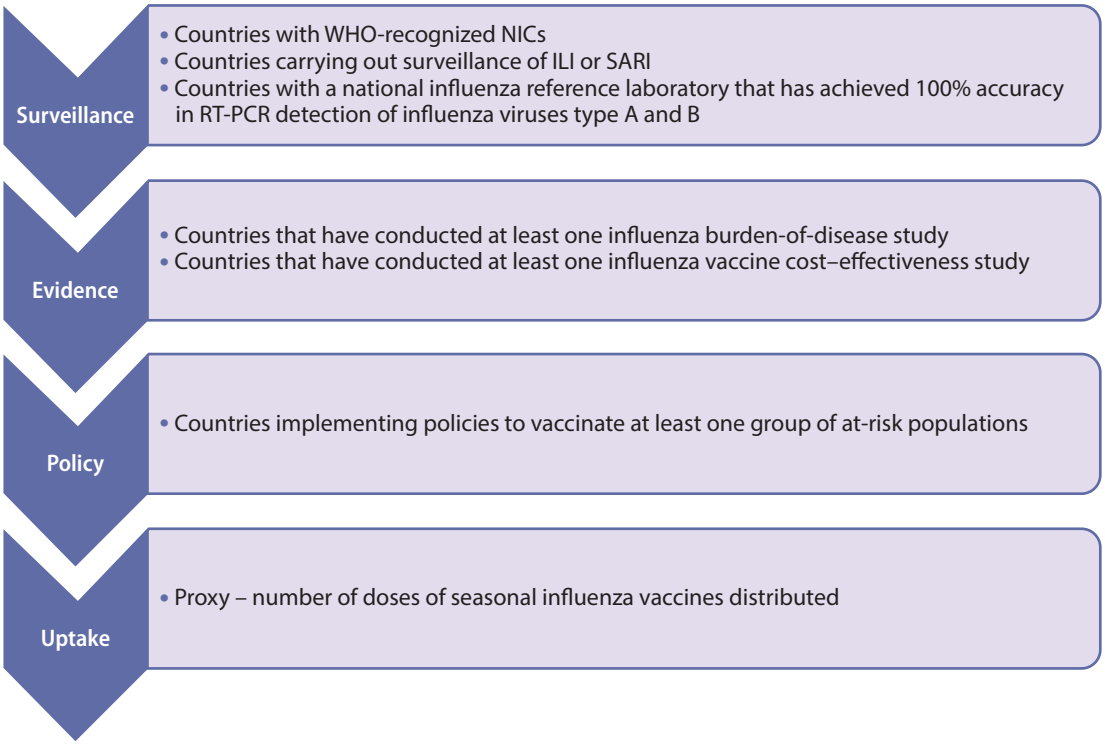
World Health Assembly resolution WHA56.19 urged Member States, "where national influenza vaccination policies exist, to establish and implement strategies to increase vaccination coverage of all people at high risk, including the elderly and persons with underlying diseases, with the goal of attaining vaccination coverage of the elderly population of at least 50% by 2006 and 75% by 2010" ***(1)***.

In response to this resolution, the first objective of the GAP was to increase the global use of seasonal influenza vaccines. Seasonal influenza vaccination builds a foundation for pandemic preparedness and strong public health systems. Through annual seasonal influenza vaccine use, Member States protect at-risk groups from severe influenza illness during seasonal epidemics, and ensure that influenza vaccine manufacturing is sustainable. Seasonal influenza immunization programmes help to keep influenza vaccine production facilities, training and protocols up to date. A lack of policies for annual procurement of seasonal influenza vaccines could jeopardize the quantity of influenza vaccines and speed with which they can be produced in the event of a pandemic. In addition, administration of seasonal influenza vaccination helps to prepare health care workers and the health system to disseminate influenza vaccines during a pandemic.

The seven indicators in this section (**Fig. 1**) focus on disease surveillance, the collection of evidence, policy development and the uptake of influenza vaccines. The WHO Global Influenza Programme provided data on NICs, and on countries that conduct surveillance on influenza-like illness (ILI) or severe acute respiratory infections (SARI) (or both), and those that have national influenza reference laboratories. The GAP Secretariat conducted a literature review to assess the number of LMIC with published influenza burden-of-disease or economic burden studies.[4] Criteria for articles to be included in that review were taken from the WHO Global Influenza Programme's *Manual for estimating disease burden associated with seasonal influenza* and the WHO Initiative for Vaccine Research (IVR) of the Department of Immunization, Vaccines and Biologicals' *Manual for estimating the economic burden of seasonal influenza*. As HIC already had data on burden of disease and cost–effectiveness, the relevant GAP indicators focus on LMIC. The Joint Reporting Form (JRF), administered by WHO and UNICEF, was the main source of data for indicators related to national seasonal influenza vaccine policies. The JRF is a self-reporting tool that is completed annually by ministries of health; it collects national information regarding immunization coverage (e.g. data on cases of vaccine-preventable diseases, vaccination campaigns, and immunization schedules and coverage). The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Influenza Vaccine Supply International Task Force provided dose distribution data for member companies; these data were used as a proxy indicator to evaluate influenza vaccine uptake.

[4] This report uses the World Bank Group's classification to define LMIC based on gross national income (GNI) per capita in 2016.

Fig. 1. Progress indicators for measuring progress towards GAP Objective 1



GAP: Global Action Plan for Influenza Vaccines; ILI: influenza-like illness; NIC: national influenza centre; RT-PCR: reverse transcriptase polymerase chain reaction; SARI: severe acute respiratory infection.

Indicator 1.1: Percentage of countries with WHO-recognized NICs

NICs are responsible for collecting and analysing virus specimens in their respective Member States, and they are critical in the global monitoring and surveillance of influenza. In addition, Member States produce key epidemiological data that support the development of influenza policy and response plans.

Virologic data (e.g. the number of influenza viruses detected by subtype) are provided by the network of NICs and other national influenza reference laboratories. These facilities make up the foundation of the WHO GISRS ***(4)*** which tracks the ever-changing nature of influenza viruses and provides recommendations regarding laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment. GISRS also acts as an alert tool for the emergence of influenza viruses with pandemic potential around the globe ***(8)***. NICs are responsible for performing preliminary analyses on collected strains and uploading the results to FluNet, a global web-based influenza surveillance tool that compiles virologic data provided by GISRS-contributing NICs and GISRS-collaborating reference laboratories ***(9)***. Country-level data are publicly available and are updated weekly.

In 2006, 79 (41%) Member States with WHO-recognized NICs contributed to GISRS (**Table 1**) ***(9)***. In 2016, 113 (58%) Member States had WHO-recognized NICs (**Table 1**) ***(9)***. Member States that do not have an NIC typically require infrastructure strengthening to create a working centre.

Indicator 1.2: Percentage of countries carrying out surveillance on ILI or SARI

The WHO Global Influenza Programme collects annual data on Member States that carry out surveillance on ILI and SARI through the FluNet and FluID systems. Launched in 1997, FluNet includes virologic data (e.g. number of influenza viruses detected by subtype) that are critical for tracking the movement of viruses globally and interpreting the epidemiological data. The data are provided remotely by WHO GISRS NICs and other national influenza reference laboratories collaborating actively with GISRS; they are also uploaded from WHO regional databases. Introduced in 2010, FluID is a global platform for data sharing that complements FluNet data by providing qualitative and quantitative data on global trends, spread, intensity and impact of influenza. All data are publicly available and updated regularly ***(10)***. As of 2016, 125 of the 194 WHO Member States consistently reported to FluNet or FluID, or both (**Table 2**).[5]

[5] Using the FluMart classification for timely and regular reporting as per the Global Influenza Programme's current definition.

Table 1. Number and percentage of Member States with a WHO GISRS NIC by WHO region, 2006–2016

WHO region	Total no. of Member States	No. of Member States		
		2006	2012	2016
African Region	47	8	12	14
Region of the Americas	35	17	21	21
South-East Asia Region	11	5	8	8
European Region	53	31	39	40
Eastern Mediterranean Region	21	7	15	15
Western Pacific Region	27	11	14	15
TOTAL	**194**	**79 (41%)**	**109 (56%)**	**113 (58%)**

AFRO: WHO Regional Office for Africa; AMRO: WHO Regional Office for the Americas; EMRO: WHO Regional Office for the Eastern Mediterranean; EURO: WHO Regional Office for Europe; GISRS: Global Influenza Surveillance and Response System; NIC: national influenza centre; SEARO: WHO Regional Office for South-East Asia; WHO: World Health Organization; WPRO: WHO Regional Office for the Western Pacific.

Table 2. Number and percentage of Member States reporting surveillance of ILI and SARI to WHO by WHO region, 2012 and 2016[a]

WHO region	Total no. of Member States	No. of Member States routinely reporting to FluNet and/or FluID	
		2012	2016
African Region	47	23	21
Region of the Americas	35	23	24
South-East Asia Region	11	7	7
European Region	53	47	48
Eastern Mediterranean Region	21	10	12
Western Pacific Region[b]	27	26	13
TOTAL	**194**	**136 (70%)**	**125 (64%)**

ILI: influenza-like illness; SARI: severe acute respiratory infection; WHO: World Health Organization.

[a] Data were collected from FluMart, which includes information from both FluNet and FluID.

[b] Within the WHO Western Pacific Region, the decrease is due to the reporting mechanism of small island nation Member States, who joined together to assess and submit their surveillance data on ILI and SARI. This change does not indicate a decrease in country capacity.

Indicator 1.3: Percentage of countries with a national influenza reference laboratory that have achieved the required level of accuracy[6] in RT-PCR detection of influenza viruses type A and B[7]

Established in 2007, the WHO External Quality Assessment Project (EQAP) tracks the quality of GISRS and national influenza reference laboratories that perform PCR diagnosis, and identifies challenges in PCR testing ***(11)***. PCR testing is an essential component of virus detection; hence, it is important to evaluate the number of Member States with a reference laboratory that achieve 100% accuracy in RT-PCR detection. EQAP is critical to maintaining the quality of GISRS detection and diagnostic capacity. In 2007, 67% of participating Member States achieved 100% accuracy in RT-PCR detection. By 2016, 89% of participating Member States had achieved this level of accuracy.

[6] The required level of accuracy in RT-PCR for this indicator is 100%.
[7] In 2010, this programme was expanded to include influenza B viruses.

Table 3. Number and percentage of Member States with national influenza reference laboratories achieving the required accuracy in RT-PCR detection by WHO region, 2007, 2012 and 2016

WHO region	No. of Member States achieving 100% accuracy/participating Member States (% achieving 100% accuracy)		
	2007	2012	2016
African Region	1/6 (17%)	17/22 (77%)	21/25 (84%)
Region of the Americas	3/4 (75%)	20/23 (87%)	21/24 (88%)
South-East Asia Region	2/3 (67%)	6/8 (75%)	6/9 (67%)
European Region	24/29 (83%)	35/44 (80%)	44/48 (92%)
Eastern Mediterranean Region	1/2 (50%)	8/11 (73%)	11/12 (92%)
Western Pacific Region	5/10 (50%)	13/13 (100%)	14/14 (100%)
TOTAL	**36/54 (67%)**	**99/121 (82%)**	**117/132 (89%)**

RT-PCR: reverse transcriptase polymerase chain reaction; WHO: World Health Organization.

Indicator 1.4: Percentage of LMIC that have conducted at least one influenza burden-of-disease study

In 2012, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization published recommendations for seasonal influenza vaccination, based on a systematic review of burden-of-disease studies and vaccine performance ***(12)***. Within these recommendations, SAGE prioritized immunization for pregnant women, followed by (not in order of priority) health care workers, people with chronic conditions, children aged 6–59 months and the elderly ***(12)***. SAGE recommended that countries with existing influenza vaccination programmes targeting any of these groups should continue to do so. In addition, SAGE emphasized the importance of ensuring that immunization of pregnant women is incorporated into such programmes (if not already done). SAGE recommended that countries without an existing influenza vaccination programme determine which risk groups to prioritize for vaccination based on the burden of disease, cost–effectiveness, feasibility and other appropriate considerations. Burden-of-disease studies provide policy-makers with insight into which portions of the population are at the highest risk for infection or most impacted by influenza. This information can be used to develop appropriate seasonal influenza vaccination policies, as well as pandemic preparedness and response plans.

The GAP Secretariat conducted a literature review for burden-of-disease publications by LMIC from 2006 to 2016. The guidance documents used included the WHO Global Influenza Programme's 2015 *A manual for estimating disease burden associated with seasonal influenza* ***(13)***, the 2016 *WHO manual for estimating the economic burden of seasonal influenza* ***(14)*** and a systematic review of the social and economic burden of influenza ***(15)***.

Fifteen (11%) LMIC had published studies between 2006 and 2010 ***(16)***. Beginning in 2014, with support from the PIP Framework Partnership Contribution, WHO provided training and support to 19 countries[8] for burden-of-influenza estimates to contribute to the development of a global burden-of-influenza estimate ***(17)***. Eight of the PIP priority countries published at least one burden-of-disease study during the GAP decade. By 2016, 53 LMIC (39%) had published at least one influenza burden-of-disease study (**Table 4**). Data are still needed for LMIC, but overall there has been notable progress at the global and national levels to better understand influenza disease burden. The Global Influenza Programme continues to support countries in generating national estimates.

Current global estimates for influenza burden of disease are outside the scope of this reporting period, but are worth noting. Annually, there are 3–5 million cases of severe influenza illness ***(18)***. In December 2017, the global estimate for annual deaths associated with respiratory disease from seasonal influenza was updated to 290 000–650 000, from the previous global estimate of 250 000–500 000. This burden-of-disease estimate was conducted by the United States of America (USA) Centers for Disease Control and Prevention (CDC), WHO's Global Influenza Programme and global health partners. The new estimate is based on more recent data from a larger, more diverse group of Member States (including LMIC), and excludes deaths from non-respiratory diseases ***(18)***.

[8] The PIP Partnership Contribution for burden of disease was provided to Albania, Armenia, Cambodia, Chile, Costa Rica, Croatia, Egypt, Georgia, Indonesia, Kyrgyzstan, Lao People's Democratic Republic, Madagascar, Republic of Moldova, Mongolia, Nepal, Oman, Senegal and Ukraine.

Table 4. Number and percentage of LMIC that have undertaken at least one influenza burden-of-disease study, by WHO region 2006–2016[a]

WHO region	No. of LMIC per region	Published 2006–2010	Published 2011–2016	No. and % of LMIC with at least one burden-of-disease study over the GAP decade
African Region	46	3	19	19 (41%)
Region of the Americas	26	5	14	15 (58%)
South-East Asia Region	11	2	3	3 (27%)
European Region	19	3	6	6 (32%)
Eastern Mediterranean Region	15	0	5	5 (33%)
Western Pacific Region	20	2	4	5 (25%)
TOTAL	**137**	**15 (11%)**	**51 (37%)**	**53 (39%)**

GAP: Global Action Plan for Influenza Vaccines; LMIC: low- and middle-income countries; WHO: World Health Organization.

[a] Several countries published during both of the periods considered. As a result, the rows cannot be directly summed for the total number of LMIC with at least one study. Countries that published during both of the periods considered are counted only once to find the total number of countries that published at least one burden-of-disease study over the GAP decade.

Table 5. Number and percentage of LMIC that evaluated the cost–effectiveness of influenza vaccination, by WHO region[a]

WHO region	No. of LMIC per region	Published 2006–2013	Published 2014–2016	No. and % of LMIC with at least one cost–effectiveness study over the GAP decade
African Region	46	1	0	1 (2%)
Region of the Americas	26	4	2	5 (19%)
South-East Asia Region	11	2	2	3 (27%)
European Region	19	2	4	6 (32%)
Eastern Mediterranean Region	15	1	0	1 (7%)
Western Pacific Region	20	1	2	3 (15%)
TOTAL	**137**	**11 (8%)**	**10 (7%)**	**19 (14%)**

GAP: Global Action Plan for Influenza Vaccines; LMIC: low- and middle-income countries; WHO: World Health Organization.

[a] Several countries published during both of the periods considered. As a result, the rows cannot be directly summed for the total number of LMIC with at least one study. Countries that published during both of the periods considered are counted only once to find the total number of countries that have published at least one burden-of-disease study over the GAP decade.

Indicator 1.5: Percentage of LMIC that have conducted at least one influenza vaccine cost–effectiveness study

Economic evaluations may help decision-makers to understand the value for money that may be rendered by the use of influenza vaccination strategies. During the decade of the GAP, WHO encouraged further research regarding seasonal influenza vaccination cost–effectiveness in LMIC.

An external literature review found that only three LMIC published articles on the economic impact of influenza vaccination programmes between 2006 and 2011 ***(19)***. The WHO GAP Secretariat conducted a literature review of economic impact publications for the period 2014–2016 from LMIC, using the 2016 Guidance on the economic evaluation of influenza vaccination ***(20)*** to determine inclusion criteria for the review. By 2016, 19 LMIC had at least one economic burden publication related to influenza (**Table 5**). Although there has been an increase in the overall number of studies regarding influenza vaccination programmes and their economic impact, research in the WHO African Region and Eastern Mediterranean Region is lacking.

Table 6. Number and percentage of Member States with a seasonal influenza vaccination policy by WHO region, 2006 and 2014

WHO region	Total no. of Member States	No. and % of Member States	
		2006	2014
African Region	47	0 (0%)	21
Region of the Americas	35	28 (80%)	24
South-East Asia Region	11	0 (0%)	7
European Region	53	31 (58%)	48
Eastern Mediterranean Region	21	5 (24%)	12
Western Pacific Region	27	10 (37%)	13
TOTAL	**194**	**74 (38%)**	**115 (59%)**

WHO: World Health Organization.

Indicator 1.6: Percentage of countries with policies to vaccinate at least one at-risk population

The data for this indicator are derived from several sources. An initial survey conducted by WHO in 2006 provided the baseline data on the status of seasonal influenza vaccination policies worldwide ***(21)***. In the following years, the WHO/UNICEF JRF was the primary source for the 2014 and 2015 data for this indicator ***(3)***. The JRF is self-reported by Member States; thus, year-to-year comparisons were challenging because Member States may or may not have submitted a JRF in a given year. Many high-income countries (HIC) from the WHO Region of the Americas and the European Region did not report influenza vaccine information in the JRF, requiring additional surveys to be conducted at the regional level ***(22-25)***.

Globally, the number of Member States with a national immunization policy increased from 74 (38%) in 2006 to 115 (59%) in 2014 (**Table 6**). Clearly, the presence of a national policy does not always correspond with an increase in influenza immunization.

HIC are more likely to have a seasonal influenza immunization policy and to devote more resources to influenza preparedness and response. In 2015, 54 (98%) HIC had a seasonal influenza immunization policy compared with 41 (79%) upper middle-income countries, 19 (37%) lower middle-income countries and one low-income country (3%) (**Fig. 2**). Also, lower-income countries often rely on financial support from international organizations (e.g. Gavi, the Vaccine Alliance) and other major funders to introduce immunization policies. Although Gavi has not worked in the influenza sector, its support strengthens the ability of national health systems to introduce immunizations. In addition, Gavi approved the development of a learning agenda of up to US$ 4 million from 2019 to 2022, to assess the feasibility and impact of routine seasonal influenza immunization of health care workers to support pandemic preparedness.

At-risk populations for influenza should be targeted by seasonal vaccination programmes. As noted above, the 2012 SAGE recommendation defined target groups for seasonal influenza vaccination: pregnant women, health care workers, individuals with specific chronic conditions, children aged 6–59 months and the elderly. In addition, SAGE recommended that countries investigate and incorporate other high-risk groups based on the burden of disease, cost–effectiveness, feasibility and other relevant considerations. As a result, a separate category for policies targeting other at-risk populations was included ***(12)***.

A review of global seasonal influenza vaccination policies in 2014 indicated that health care workers and adults with chronic diseases were the most frequently targeted at-risk populations (**Fig. 3**) ***(3)***. In 2014, children were the least frequently mentioned at-risk group in national seasonal influenza vaccination policies.

Fig. 2. Percentage of countries with a national seasonal influenza immunization policy by income classification, 2014

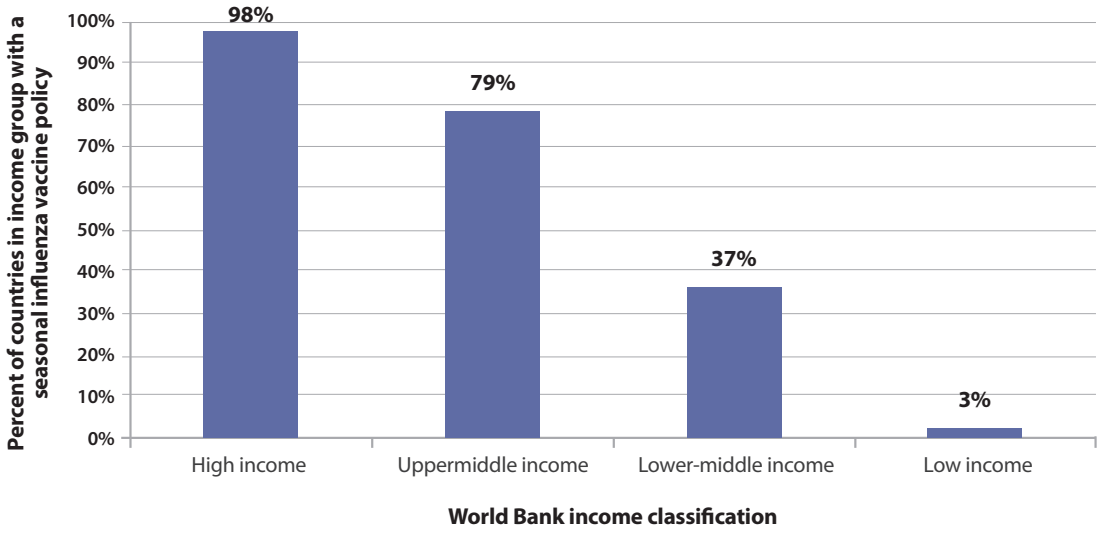
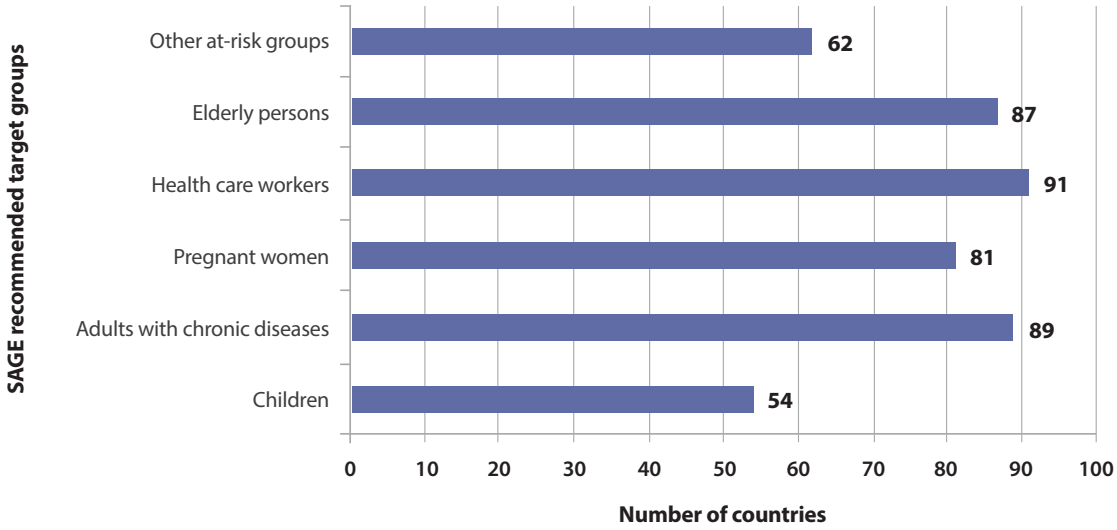


Fig. 3. Global distribution of national influenza immunization policy target groups, 2014[a]



SAGE: Strategic Advisory Group of Experts on Immunization.

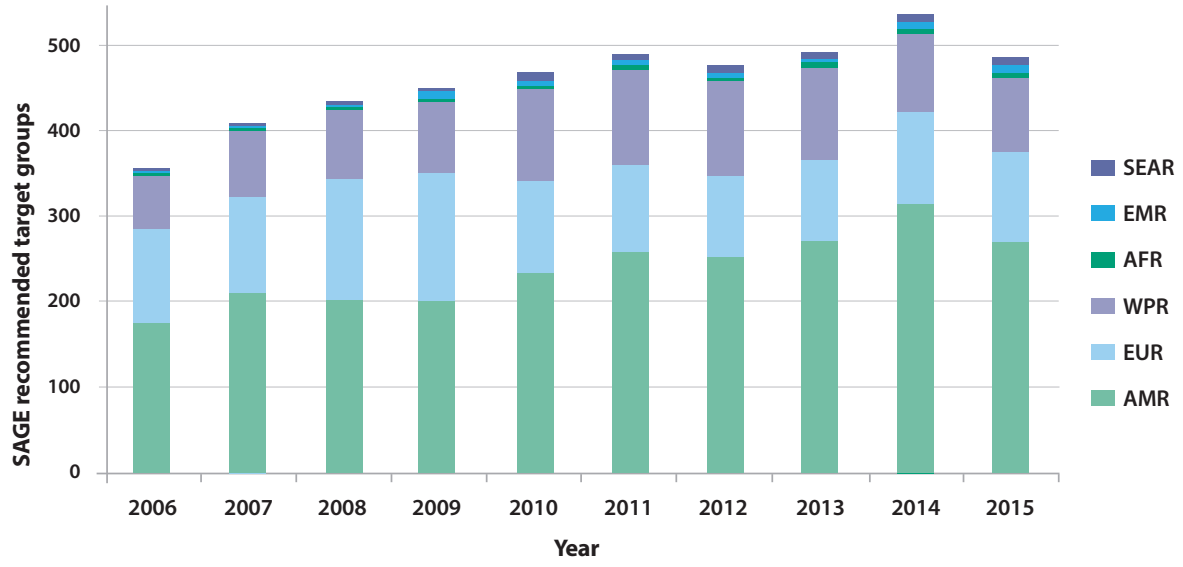
[a] In their national seasonal influenza immunization plans, countries may target more than one at-risk group.

Table 7. Number of seasonal influenza vaccine doses distributed by IFPMA members by WHO region, 2006, 2012 and 2015

WHO region	Number of seasonal influenza vaccine doses distributed by IFPMA members (millions)		
	2006	2012	2015
African Region	2.0	3.9	4.8
Region of the Americas	173.2	252.0	267.7
South-East Asia Region	1.3	7.6	9.2
European Region	110.3	94.1	106.2
Eastern Mediterranean Region	3.3	5.2	10.9
Western Pacific Region	63.8	111.9	87.1
TOTAL	**353.9**	**474.7**	**485.9**

IFPMA: International Federation of Pharmaceutical Manufacturers and Associations; WHO: World Health Organization.

Fig. 4. Number of seasonal influenza vaccine doses distributed by IFPMA members by WHO region, 2006–2015



Indicator 1.7: Percentage of targeted at-risk populations vaccinated

This indicator has been removed from the 2006–2016 global progress report owing to a lack of reliable data.

Indicator 1.8: Number of doses of seasonal influenza vaccine purchased or procured

Currently, there is no global mechanism to measure influenza vaccine uptake. However, the number of doses of seasonal influenza vaccine purchased is used as a proxy indicator to evaluate uptake. IFPMA Influenza Vaccine Supply International Task Force provided the number of seasonal influenza vaccine doses distributed by its member companies (**Table 7**, **Fig. 4**) ***(26)***. While the following data do not include non-IFPMA manufacturers, they provide a robust overview of the trends in dose distribution over the last 10 years.

The global total of doses distributed increased significantly between 2006 and 2015 (from 353.9 million to 485.9 million doses). Consistently, the WHO Region of the Americas, European Region and Western Pacific Region have received the majority of doses distributed.

Progress indicators for GAP Objective 1: Summary

The summary of GAP Objective 1 demonstrates noticeable improvements across the seven indicators (**Table 8**).

Table 8. GAP progress indicators for Objective 1

GAP progress indicator		2006 (baseline)	2012	2016
1.1	Percentage of countries with an NIC	41%	56%	58%
1.2	Percentage of countries reporting surveillance data of ILI and SARI	N/A	70%	64%
1.3	Percentage of participating Member States achieving the required level of accuracy in RT-PCR diagnostic tests for influenza viruses	67% (2007)	82%	89%
1.4	Percentage of LMIC that have completed an influenza burden-of-disease study	4% (2005)	11% (2010)	39%
1.5	Percentage of LMIC that have conducted an evaluation of the cost–effectiveness of seasonal influenza vaccination	2% (2005)	8% (2013)	14%
1.6	Percentage of countries with a policy to vaccinate at least one at-risk population group	38%	N/A	59% (2014)
1.7	Percentage of targeted at-risk populations vaccinated (removed owing to lack of reliable data)	N/A	N/A	N/A
1.8	Number of doses of seasonal influenza vaccines distributed (millions of doses)	354	475	486

GAP: Global Action Plan for Influenza Vaccines; ILI: influenza-like illness; LMIC: low- and middle-income countries; NA: not available; NIC: national influenza centre; RT-PCR: reverse transcriptase polymerase chain reaction; SARI: severe acute respiratory infection.

PROGRESS UNDER

2 Objective 2: Increase vaccine production capacity & strengthen national regulatory capacity to assess & approve influenza vaccines

TARGET: Increase influenza vaccine production and regulatory capacity through technology transfers to improve global access to influenza vaccines.

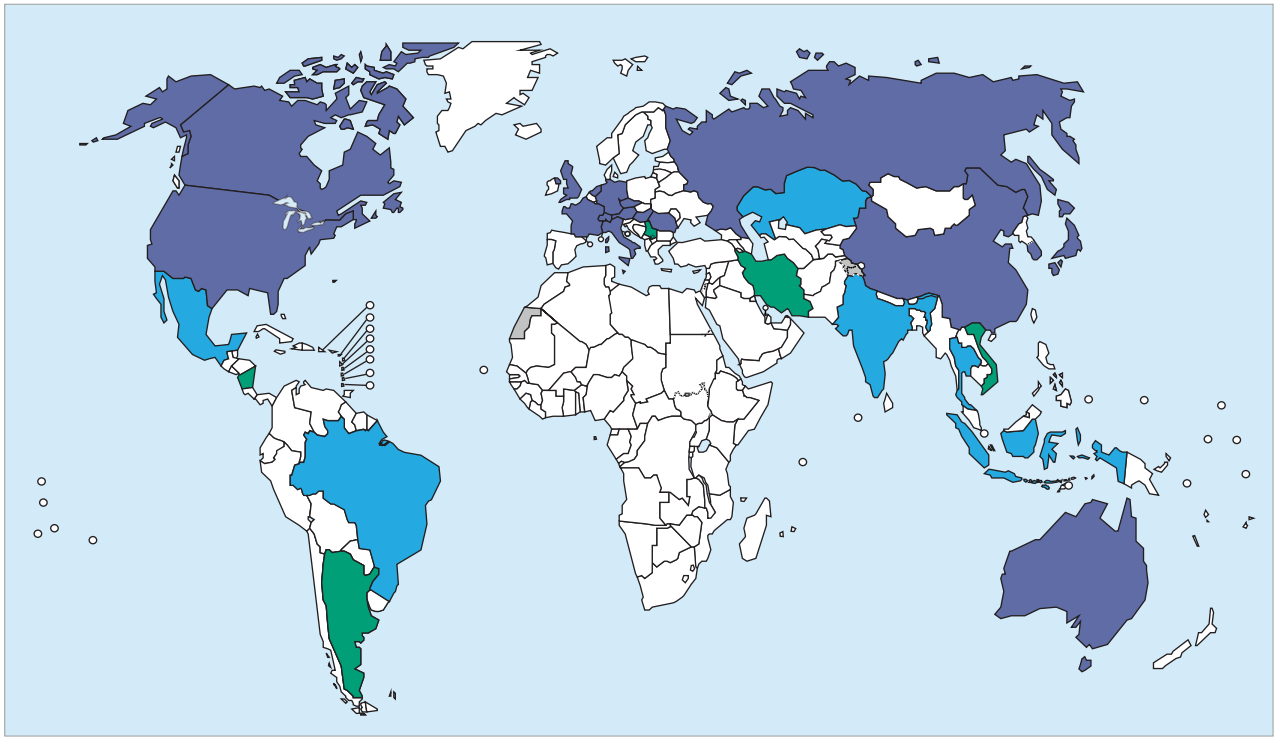
Historically, influenza vaccine manufacturing occurred nearly exclusively in HIC. The GAP advocated for the establishment of production capacity in LMIC to improve equitable distribution of influenza vaccines and regional response time in the event of a pandemic. As the following indicators demonstrate, the decade of the GAP resulted in a global expansion of influenza vaccine production.

With support from the Biomedical Advanced Research and Development Authority (BARDA) within the USA Department of Health and Human Services (HHS), the Government of Japan and other key stakeholders, WHO facilitated technology transfer to 14 LMIC, to establish or expand influenza vaccine manufacturing capacity. The premise of this technology transfer was that countries with sustainable seasonal influenza manufacturing capacity could switch to pandemic influenza vaccine production in the event of a pandemic outbreak. NRAs are critical to the evaluation and licensing of vaccines before their market release; therefore, WHO and its partners supported these Member States in strengthening their regulatory systems.

Six of the countries receiving technology transfer have licensed eight pandemic influenza vaccines (two are WHO prequalified) and three seasonal vaccines (one is WHO prequalified). Additional vaccine licensures are expected before 2020. The GAP Secretariat estimated that the technology transfer of influenza vaccine production capacity to LMIC will generate an additional 1.135 billion pandemic doses ***(6)***.

Data for these indicators were collected from publications, WHO surveys, and information from IFPMA members as well as other vaccine manufacturers ***(28, 29)***. The global landscape of domestic influenza vaccine production since 2006 is represented by region in **Fig. 5**.

Fig 5. Expansion in domestic influenza vaccine production capacity since 2006 [9]



Countries producing influenza vaccines in 2006
Countries who established & licensed locally produced influenza vaccines between 2006 and 2016
Countries establishing locally produced influenza vaccines with first approval expected by 2019
Not applicable
Data not available

Indicator 2.1: Number of countries with operational seasonal influenza vaccine production capacity

Pandemic influenza preparedness relies on consistent production of and access to seasonal influenza vaccines. A sustainable and adequately scaled seasonal influenza vaccine manufacturing base is essential for timely and rapid production scale-up in response to a pandemic. During the GAP decade, the number of Member States with seasonal influenza vaccine production capacity fluctuated, owing to the emergence of new manufacturers in the WHO Region of the Americas, South-East Asia Region and Western Pacific Region, and to consolidations of influenza vaccine manufacturers in the European Region (**Table 9**). Additional manufacturers in Member States in the WHO Eastern Mediterranean Region, the European Region, South-East Asia Region and Western Pacific Region are anticipated to license influenza vaccines.

Facilities that only have fill/finish capacity will not be able to contribute to the pandemic influenza vaccine doses for distribution. As a result, **Table 9** does not include fill/finish facilities. In 2006, of the 17 Member States producing influenza vaccine, only one (6%) was an LMIC, and one of the 15 Member States with seasonal influenza vaccine production capacity in place was an LMIC. By 2016, five (33%) of the Member States with influenza vaccine production capacity were LMIC; this increase was achieved through the GAP technology transfer mechanism.[10]

[9] The boundaries and names shown and designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area, or of its authorities or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

[10] Not all GAP grantee countries with a licensed product were producing influenza vaccine for use each year.

Table 9. Number of Member States with seasonal influenza vaccine production capacity in place by WHO region, 2006, 2011 and 2016[a]

WHO region	No. of Member States achieving 100% accuracy/participating Member States (% achieving 100% accuracy)		
	2006	2011	2016
African Region	0	0	0
Region of the Americas	2	2	4
South-East Asia Region	0	1	1
European Region	12	13	6
Eastern Mediterranean Region	0	0	0
Western Pacific Region	3	4	4
TOTAL	**17**	**20**	**15**

WHO: World Health Organization.

[a] Data were collected from the USA Food and Drug Administration, the European Medicines Agency and the International Federation of Pharmaceutical Manufacturers and Associations. Publicly available data were also collected from individual manufacturers.

A 2015 survey estimated global seasonal influenza production to be 1.467 billion doses ***(5)***. Estimates of total potential pandemic vaccine production capacity are generally derived from estimates of seasonal trivalent and quadrivalent influenza vaccine capacity. Because a pandemic vaccine would be monovalent, the production capacity employed on the second, third and fourth strains included in seasonal vaccines could be used to generate additional pandemic vaccine doses. This multiplicative factor may also consider other assumptions, such as production yield or whether adjuvant (antigen-sparing) technology is used ***(5)***.

Although global seasonal influenza vaccine production capacity decreased slightly in the final years of the GAP, potential pandemic influenza vaccine production capacity grew substantially from 2006 to 2016. This change can be explained by the increase in manufacturers producing quadrivalent vaccine rather than trivalent, as well as the introduction of new manufacturers in the WHO South-East Asia Region and Region of the Americas. In addition, more manufacturers are using and developing antigen-sparing technologies (e.g. adjuvants); such technologies increase the number of potential pandemic doses available. The reported global potential pandemic dose production for all countries increased from an estimated 4.260 billion doses in 2011 to 6.176 billion doses in 2013. A 2015 estimate predicted pandemic influenza vaccine production capacity to be 6.372 billion doses ***(5)***.

Regional influenza vaccine production capacity continues to evolve, particularly as capacity stabilizes in LMIC. The technology transfer of influenza vaccine production capacity to LMIC is expected to generate up to 1.135 billion pandemic influenza vaccine doses ***(6)***. To sustain and expand production, Member States must develop and implement policies to vaccinate at-risk groups. These policies should be based on estimates of burden of disease and cost–effectiveness. Ensuring a sustained market for seasonal influenza offers a pathway to pandemic vaccine production in the event of an outbreak.

Indicator 2.2:[11] Cumulative number of LMIC that have conducted a sustainable local production or procurement of influenza vaccine assessment

Sustainable local production and procurement of influenza vaccines requires a coherent and coordinated approach to industrial, economic and public health policies, brought forward through transparent and joint actions of all stakeholders (e.g. government agencies, manufacturers, international multilateral institutions and donor communities) ***(30)***. In 2013, WHO, HHS and stakeholders identified key components of sustainable local production to assist countries with mapping and analysing their influenza policy environment ***(30)***. This sustainability checklist addresses six areas: policy environment and health system; influenza surveillance, early detection and evidence; product development and manufacturing; product approval and regulations; communication for influenza vaccination; and financing.

By undergoing a sustainability assessment, Member States identify their national strengths and the opportunities to improve the local production environment, with guidance from WHO. Although the six key components of sustainability are applicable globally, specific contexts and products result in a unique blend of recommendations for each Member State that conducts an assessment. Hence, the checklist continues to evolve and be enriched by national case studies, as well as by continued consultations with experts ***(31)***. Country assessments began in 2014 and will continue to be conducted to support the sustainable local production of influenza vaccines.

[11] Indicator 2.2, "Number of LMIC vaccine manufacturers with annual supply agreements in place for seasonal influenza vaccines" from the 2013 GAP progress report, was replaced by "Cumulative number of LMIC that have conducted a sustainable local production or procurement of influenza vaccine assessment". This revision was undertaken because of the lack of data regarding the original indicator, and to highlight one of the key mechanisms the GAP Secretariat developed to support sustainable seasonal influenza vaccine introduction in LMIC.

Table 10. Number of LMIC that conducted the sustainability assessment checklist for local production or procurement

Year	No. of LMIC that conducted the sustainability assessment checklist for local production or procurement
2014	1 (Indonesia)
2015	2 (Mexico, South Africa)
2016	3 (Brazil, Morocco, Viet Nam)
2017	1 (Thailand)
2018	1 (Serbia)

LMIC: low- and middle-income countries.

Indicator 2.3: Number of manufacturers using or developing antigen-sparing technologies (adjuvants) or high-yield processes (live or recombinant technologies) for influenza vaccines

The use of antigen-sparing or high-yield technologies and processes allows for increased production of influenza vaccine doses in the event of a pandemic. Adjuvants, live attenuated influenza vaccine (LAIV), and recombinant technologies – which include the most recent virus-like particle (VLP) vaccines – fall into these categories. A new entry in vaccine development, VLPs are multiprotein structures that mimic the organization and conformation of authentic native viruses but lack the viral genome, potentially allowing for production of safer and more cost-effective vaccines ***(32)***.

The GAP fostered a research environment that encouraged development of improved influenza vaccines. In 2006, only three manufacturers were using such technologies.[12] At the end of 2012, eight manufacturers were using these processes to produce influenza vaccines, with one manufacturer using both LAIV and adjuvant technology. As of 2016, 14 manufacturers were developing or employing antigen-sparing or high-yield processes for influenza vaccine production (**Table 11**). Two of these manufacturers (Green Cross and Serum Institute of India) received direct support through the GAP technology transfer mechanism.

Table 11. List of vaccine manufacturers employing or developing antigen-sparing (adjuvants) or high-yield processes, 2016[a]

Manufacturer	2012 process (antigen-sparing or high-yielding)	2016 process (antigen-sparing or high-yielding)
Cadila Pharmaceuticals		VLP
BCHT		LAIV
Denka Seiken		Adjuvant
Fluart		Adjuvant
GSK Biologicals	Adjuvant	Adjuvant
Government Pharmaceutical Organization	LAIV	LAIV
Green Cross	Adjuvant	Adjuvant
Kitasato		Adjuvant
MedImmune	LAIV	LAIV
MicroGen	Adjuvant	Adjuvant
MicroGen	LAIV	LAIV
Novartis[b]	Adjuvant	
Protein Sciences		Recombinant
Serum Institute	LAIV	LAIV
Seqirus		Adjuvant
Sinovac Biotech		Adjuvant

LAIV: live attenuated influenza vaccine: VLP: virus-like particle.

[a] Manufacturers qualify for inclusion if they are approved (i.e. licensed) to use, or are at an advanced stage of development (phase III) of, any of the listed technologies. Antigen-sparing technologies refer to oil-in-water emulsions only (e.g. MF59 and ASO3).

[b] Seqirus acquired Novartis's influenza vaccine portfolio in 2015.

[12] GSK and Novartis had access to their propriety dose-sparing adjuvants, and MedImmune's LAIV high yield (FluMist) was approved in the USA market.

Indicator 2.4: Proportion of LMIC manufacturing or planning to produce influenza vaccines with an NRA functional against WHO indicators for vaccine prequalification

NRAs are national agencies responsible for the regulation of products released to the market for public distribution and use. In particular, they evaluate the quality, safety and effectiveness of products being produced or distributed within their national borders. Since the publication of the 2014 GAP progress report *(2)*, WHO has adopted a new model for regulatory system strengthening – the Global Benchmarking Tool (GBT) – which assesses NRAs according to their level of maturity. The GBT assessments of NRA capacities highlight gaps in capacity, and produce recommendations to address these gaps *(33)*. The GBT assessment is necessary to enable WHO prequalification of locally produced vaccines.

With this new benchmarking tool, nine indicators of a mature NRA are assessed:

- national regulatory system
- registration and marketing authorization
- vigilance
- market surveillance and control
- licensing premises
- regulatory inspection
- laboratory access and testing
- clinical trial oversight
- NRA lot release (included only in vaccine assessment).

As shown below (**Table 12**), each maturity level is scaled from Level 1, indicating that there is no formal approach, to Level 5, indicating the best in class performance. Level 3 and above indicate the NRA has the maturity to regulate domestic production of vaccines.

The GAP advocated for regulatory system strengthening, to permit local production and procurement of influenza vaccines. During the GAP decade, the regulatory system strengthening team implemented the GBT and transitioned from evaluating NRAs by functionality to assessing them by their maturity level *(34)*.[13]

Table 12. Maturity levels for NRAs according to the GBT

Maturity level	Corresponds to
Level 1	No formal approach – no systematic approach evident, no results, poor results or unpredictable results
Level 2	Reactive approach – problem or corrective-based systematic approach; minimum data on improvement results available
Level 3	Stable formal system approach – systematic process-based approach, early stage of systematic improvements; data available on conformance to objectives and existence of improvements
Level 4	Continual improvement emphasized – improvement process in use; good results and sustained improvement trends
Level 5	Best in class performance – strongly integrated improvement process; best in class benchmarking results demonstrated

GBT: Global Benchmarking Tool; NRA: national regulatory authority.

[13] Before the introduction of the GBT system, NRAs were evaluated as functional or non-functional. The GBT system was introduced in 2013 and evaluates NRAs by levels of maturity.

Table 13. Number and percentage of LMIC influenza vaccine manufacturers producing or planning to produce influenza vaccines with functional/mature NRA by WHO region, 2006 and 2016

WHO region	No. of LMIC with influenza vaccine(s) licensed or in clinical development	No. and % LMIC with influenza vaccine(s) licensed or in clinical development and a functional NRA	
		2006	2016
African Region	1[a]	0 (0%)	0 (0%)
Region of the Americas	3	1 (33%)	2 (67%)
South-East Asia Region	3	2 (67%)	3 (100%)
European Region	4	0 (0%)	0 (0%)
Eastern Mediterranean Region	2	0 (0%)	2 (100%)
Western Pacific Region	3[b]	1 (50%)	3 (100%)
TOTAL	**16**	**4 (25%)**	**10 (63%)**

LMIC: low- and middle-income countries; NRA: national regulatory authority; WHO: World Health Organization.
[a] One previously enrolled LMIC in the African Region formally withdrew from the GAP technology transfer after 2013.
[b] One LMIC in the Western Pacific Region joined the GAP technology transfer post 2013.

Progress indicators under GAP Objective 2: Summary

The four progress indicators demonstrate overall success over the past 10 years (**Table 14**).

Table 14. GAP progress indicators for Objective 2

GAP progress indicator		2006 (baseline)	2012	2016
2.1	Number of countries with seasonal influenza vaccine production capacity	17	20 (2011)	15
2.2	Cumulative number of LMIC that have conducted a sustainable local production or procurement of influenza vaccine assessment	0	0	6
2.3	Number of vaccine manufacturers using or developing antigen-sparing technologies or high-yield processes	3	8	14
2.4	Number of LMIC with existing or planned vaccine production capacity that also have a fully functional/mature NRA	4	9	10

GAP: Global Action Plan for Influenza Vaccines; LMIC: low- and middle-income countries; NRA: national regulatory authority; WHO: World Health Organization.

PROGRESS UNDER

3 Objective 3: Develop more effective vaccines using new technologies

TARGET: By 2016 to have under license or in advanced clinical development new influenza vaccines that are either higher yielding, and/or faster to produce, and/or broader in protection, and/or with a longer duration of protection compared with the currently licensed vaccines.

The aim of this objective was to assess the development of improved influenza vaccines. The total number of influenza vaccines under development has steadily increased, from 59 in 2008 to 98 in 2016 (**Table 15**). A relatively large number of products are in early research phases, and the number of products achieving market approval per year has increased. This may reflect improvements in resources available to complete the clinical review process, ability to demonstrate efficacy in clinical trials or a materialized proof of concept.

Indicator 3.1:[14] Number of influenza vaccines under development

The GAP advocated for the development of improved influenza vaccines. BARDA conducted landscape analyses spanning from November 2008 to August 2016 that demonstrate the research and development trends for seasonal and pandemic influenza vaccine products (**Table 15**) ***(35, 36)***. The data are not cumulative, but vaccines may linger in research phases over multiple years.

Table 15. Number of influenza vaccines under development by research phase, 2008–2016

Seasonal and pandemic influenza vaccines, by research phase	No. of vaccines under development		
	2008	2013	2016
Preclinical	17	33	32
Phase I	18	14	16
Phase II	8	14	16
Phase III	5	4	3
Market approved or licensed[a]	11	30	31
TOTAL	**59**	**95**	**98**

[a] Similar products from small-scale manufacturers are not included.

[14] The data available did not indicate the novelty of the influenza products; thus, this indicator was revised from "number of novel products under development" in the 2013 GAP progress report to "number of influenza vaccines under development".

Indicator 3.2: Number of clinical trials included in the publicly available database

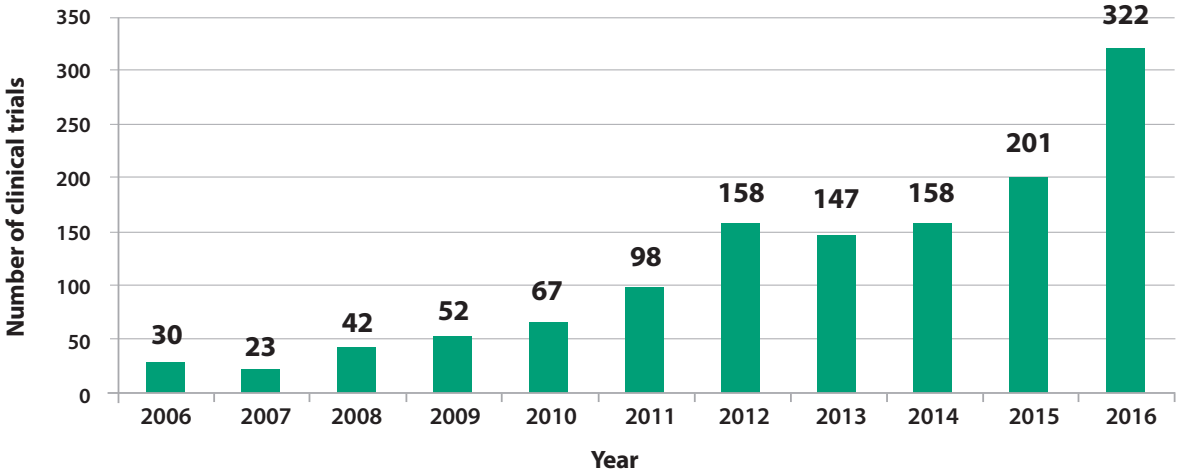
Historically, WHO has maintained a publicly accessible database with clinical trials for both pandemic or pre-pandemic and seasonal influenza vaccines. The 2006–2013 GAP progress report made use of this database; however, because the database has not been consistently maintained, to capture the full decade of the GAP, this review was conducted through ClinicalTrials.gov (a global database of privately and publicly funded clinical studies). The review included all seasonal and pandemic influenza vaccine clinical trials, and it identified an increase in the number of clinical trials included in the publicly available database, from 30 trials in 2006 to 322 trials in 2016 (**Fig. 6**) ***(7)***. This increase reflects the growing interest and investment in influenza vaccine research and development throughout the decade of the GAP.

Indicator 3.3: Number of influenza vaccines licensed or in an advanced clinical development phase by technology type[15]

The traditional egg-based influenza vaccine has many limitations (e.g. the time needed to produce the vaccine and available supply of eggs). Recognizing these limitations, the GAP stimulated a global push for improved influenza vaccine production methods and technologies. For example, cell-based and recombinant vaccine production techniques offer the ability to scale up vaccine production by reducing the above-mentioned limitations, which act as bottlenecks. With the addition of new VLPs that mimic authentic viruses, production may become safer and more cost-effective. LAIV may provide broader and higher levels of protection among healthy preschool and school-aged children ***(37)***.

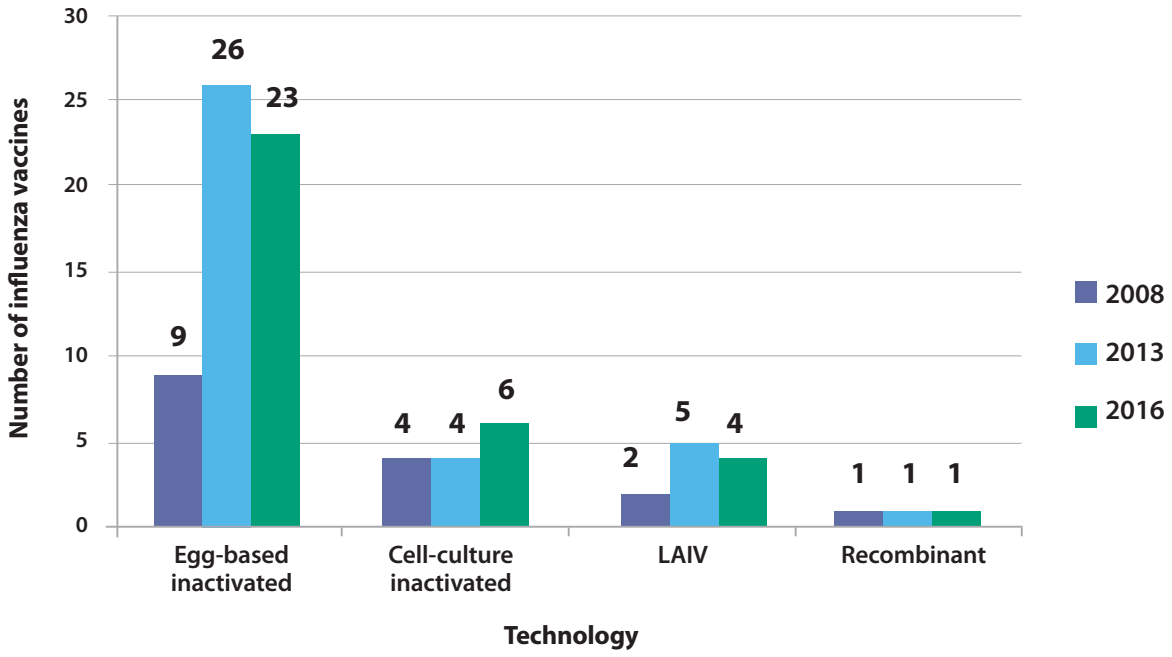
As of 2016, most of the vaccines that were licensed or in advanced-phase clinical trials were egg based. Five cell-culture and three LAIV products were available on the market for seasonal and pandemic uses, and one recombinant seasonal influenza vaccine was licensed, but no recombinant pandemic vaccines had reached advanced-phase trials. Universal, vector or nucleic acid technology had not undergone advanced-phase clinical trials (**Fig. 7**) ***(36)***.

Fig. 6. Number of seasonal and pandemic influenza vaccine clinical trials



[15] To provide the full landscape of influenza vaccine product development, this indicator was modified from "Number of new influenza vaccines licensed or in an advanced clinical development phase that are either high yielding and/or faster to produce, and/or broader in protection and/or with a longer duration of protection compared to current licensed vaccines" to "number of influenza vaccines licensed or in an advanced stage of clinical development by technology type".

Fig. 7. Number of seasonal vaccine products licensed or in phase III, 2008, 2013 and 2016



LAIV: live attenuated influenza vaccine: VLP: virus-like particle.

Progress indicators under GAP Objective 3: Summary

During the GAP, considerable progress was made (as discussed above) in research and development of both seasonal and pandemic influenza vaccines and products (**Table 16**). In particular, the number of registered clinical trials for influenza vaccine and the number of influenza vaccines in development or recently licensed increased significantly over the decade of the GAP.

Table 16. GAP progress indicators for Objective 3[a]

GAP progress indicator		2006 (baseline)	2012	2016
3.1	Number of influenza vaccines under development	59 (2008)	95 (2013)	98
3.2	Number of clinical trials included in the publicly available database	30	158	322
3.3	Number of influenza vaccines licensed or in an advanced stage of clinical development by technology type	16 (2008)	36 (2013)	35 (2016)

GAP: Global Action Plan for Influenza Vaccines.

[a] The data across these three indicators may be cumulative, depending on the length of time for development or licensing.

GAP TARGET INDICATOR

4 Proportion of the global population covered by pandemic influenza vaccines which provide adequate protection and which have been produced within 6 months of the transfer of the vaccine master seed to industry

The primary focus of the GAP was to ensure production capacity to vaccinate 70% of the world's population in the event of a pandemic. **Table 17** and **Table 18** illustrate the global coverage during a pandemic that requires one or two doses of vaccine, depending on the scenario.

The GAP target indicator was intended to assess the 6-month production capacity, but this report provides an analysis for annual production. However, manufacturers provided the GAP Secretariat with their annual seasonal influenza vaccine production capacity.[16] As a result, providing an annual analysis of pandemic influenza vaccine production capacity offers a more comprehensive picture of the global potential capacity. The estimates given below begin with the production of vaccine.

Coverage estimates were calculated for 2015[17] based on manufacturers' production capacity. The production capacity was calculated with the underlying assumption that one dose of a trivalent seasonal vaccine would produce three doses of a pandemic influenza vaccine ***(5)***. Thus, Table 17 reflects the annual coverage capacity following the announcement of a pandemic that requires two doses of vaccine. Because these calculations assess the production capacity and do not take into consideration quadrivalent capacities, these estimates may not fully include the benefits of novel vaccines using antigen-sparing and high-yield technologies.

To achieve the GAP target goal for an influenza pandemic requiring two doses of vaccine, 10.224 billion doses would be required. However, global pandemic influenza vaccine capacity was only 6.372 billion doses in 2015, almost two thirds of the required doses. An additional 3.852 billion doses would have been required to immunize the target global population with two doses of pandemic influenza vaccine in 2015 (**Table 18**).

16 The Global Influenza Programme has convened global experts to review and streamline the switch process to accelerate the availability of pandemic influenza vaccines.
17 Data on global production capacity were most recently available in 2015.

Table 17. Global coverage estimates in the event of a pandemic that requires two doses of influenza vaccine, 2015

	Global population (billions)	Target: 70% of global population (billions)	Number of doses required to vaccinate population target with two doses (billions)	Annual potential pandemic influenza vaccine production capacity (billions)	Additional doses required to reach target
Global coverage	7.303 people	5.112 people	10.224 doses	6.372 doses	3.852 doses

Table 18. Global coverage estimates for a pandemic that requires one dose of influenza vaccines, 2015

	Global population (billions)	Target: 70% of global population (billions)	No. of doses required to vaccinate target population with one dose (billions)	Annual potential pandemic influenza vaccine production capacity (billions)
Global coverage	7.303 people	5.112 people	10.224 doses	6.372 doses

In the event of a pandemic that requires one dose of influenza vaccine, the GAP target of having sufficient vaccine to immunize 70% of the global population was feasible in 2015. As Table 18 demonstrates, the potential pandemic influenza vaccine capacity of 6.372 billion doses was sufficient to vaccinate an additional 1.26 billion individuals beyond the GAP target. However, these analyses depict the best-case production capacity of influenza vaccine under pandemic conditions, with vaccine production anticipated to take about 5 months, meaning that the vaccine would not be available at the onset of a pandemic outbreak.

In addition to encouraging expanded influenza vaccine production, WHO, under the PIP Framework, signed standard material transfer agreements (SMTA2s) with manufacturers to donate and provide affordably priced influenza vaccines, antiviral drugs and ancillary supplies. As of 2016, under the SMTA2s, 300 000 vaccines had been secured in the event of a pandemic ***(38)***. Additional SMTA2s continue to be negotiated with industry.

Summary

The GAP was the catalyst for a significant expansion in global influenza vaccine manufacturing capacity, particularly within LMIC. Lessons learned throughout the decade of the GAP reiterate the importance of a continued focus on sustainable influenza vaccine production. The response to an influenza pandemic will be effective only if sufficient pandemic vaccines are produced and distributed in a timely manner. For pandemic influenza preparedness, experience shows that seasonal influenza vaccine production facilities must be operational to be able to switch to producing pandemic vaccines. Sustaining the influenza vaccine manufacturing capacity in LMIC increases equitable access to influenza vaccines and expands the global capacity to respond to seasonal and pandemic influenza. In addition to sustaining local influenza vaccine production, countries can prepare their health systems for future influenza pandemics by developing and maintaining seasonal influenza policies and programmes.

The GAP AG identified the following issues as requiring global coordination and WHO's leadership:

- manufacturers in developing countries still require technical assistance to bring their fledgling capacity online, and business acumen to ensure that their technical efforts are sustainable and will be in place when the next pandemic occurs;
- research into and development of improved influenza vaccines and vaccination strategies need to be coordinated, to ensure that products meet public health needs, and to facilitate development and licensing;
- the root causes of influenza vaccine hesitancy need to be identified and addressed in all countries, because they undermine vaccine uptake and threaten the sustainability of current production levels;
- more evidence is needed on vaccine effectiveness in specific risk groups;
- an expert review of the assumptions that led to the definition of the three GAP approaches would be useful, to identify innovative ways of addressing global preparedness for pandemic influenza and to point the way forward; and
- WHO should maintain an influenza vaccine coordination role or mechanisms to ensure that it can continue to provide technical assistance, oversight and engagement with stakeholders.

Following the closing of the GAP, WHO has continued activities in all recommended areas of work. In addition, WHO has continued to conduct sustainability assessments with LMIC that are producing or procuring influenza vaccines to support enabling environments for influenza vaccines.

WHO has launched the Global Influenza Strategy 2019–2030, a coordinated organization-wide approach to influenza preparedness and response that aims to attain the highest possible influenza prevention, control and preparedness, to contribute to health for all people. This strategy builds on GAP's work to encourage the development of better global tools, as well as the strengthening of country capacities to combat seasonal and pandemic influenza.

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