Global influenza vaccine distribution survey demonstrates urgency of implementation of objective 3 of WHO influenza strategy 2019-2030.

Authors

Palache A[a], Tsai T[b], Yuri Vasiliev[c], Abelin A[d], Hollingsworth R[e], Taylor B[f], Barbosa P[g], on behalf of the IFPMA Influenza Vaccine Supply (IFPMA IVS) task force.

Affiliations

[a] Consultant at Abbott, C.J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands;

[b] Takeda Vaccines, 40 Landsdowne Street, Cambridge, MA 02139;

[c] St. Petersburg Research Institute of Vaccines and Sera, Svobody st. 52, Krasnoe Selo, 198320, Russian Federation;

[d] Sanofi Pasteur, 2 Ave Pont Pasteur, Lyon 69007, France;

[e] Sanofi Pasteur, 1 Discovery Dr, Swiftwater, PA 18370, USA ;

[f] Seqirus Vaccines, Renaissance Way, Speke, Liverpool L24 9JW, UK;

[g] International Federation of Pharmaceutical Manufacturers and Associations, Ch. des Mines 9, P.O. Box 195, 1211 Geneva 20, Switzerland

Abstract

The World Health Organization's (WHO) Global Action Plan for influenza vaccines (GAP) and Global Influenza strategy 2019-2030 (objective 3) called for the expansion of seasonal influenza prevention. In 2008, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Influenza Vaccine Supply International Task Force's (IVS) developed a methodology to track progress in the prevention of seasonal influenza. Data from 200 countries were confidentially collected and aggregated by the IFPMA Secretariat, and combined with previous IFPMA IVS survey data (2004–2015). A "hurdle" rate, defined as the number of doses per 1,000 population required to reach the proportion of the population 65 years and older, was used to assess vaccination coverage of the primary target group, the elderly. In this fifth update of the IFPMA IVS survey, we found: the number of doses distributed in 2017 were similar to the numbers distributed in 2012; the number of countries using any seasonal influenza vaccine in 2017 was similar to the number first achieved in 2008; the rate of dose distribution per 1,000 persons was similar to the rate first achieved between 2007 and 2008; and the proportion of countries achieving the hurdle rate in 2017 was the second lowest for any year in the survey. These data provide strong evidence that following initial gains in dose distribution, between 2004 and 2008, progress in the control and prevention of seasonal influenza has stagnated or regressed everywhere except in the Americas region. This survey highlights that policies and tactics to increase vaccination coverage have to date been unsuccessful outside of the Americas. It provides the WHO's Global Influenza strategy 2019-2030 with strong evidence that the highest importance and urgency should be attached to strategic goal 3.

Keywords: seasonal influenza; vaccination policy; vaccination coverage rates; pandemic preparedness; vaccine recommendations; monitoring and evaluation.

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1. Introduction

According to the World Health Organization (WHO) Global Influenza strategy 2019-2030[1], many experts believe that an influenza pandemic is the greatest threat to global public health. The 1918 - 1919 influenza pandemic led to a "dramatic decline in life expectancy in many countries at the time of the pandemic… [leading] to fundamental changes in public health and health care systems". The paper also notes that the occurrence of another influenza pandemic is inevitable, and could well occur within the time frame of the strategy. Perhaps most significantly, the document notes that because of globalization, urbanization and mobility, the next pandemic will spread further and faster. Of note, the world population in 1920 was estimated at 1.86 billion[2], about one quarter of the United Nations' Population Division's estimate of 7.79 billion for 2020[3].

Since the 2009 H1N1 pandemic, significant steps have been taken to improve a subsequent global response[1]: advances to International Health Regulations (2005)[4] compliance and capacities for pandemic preparedness and health security; expansion of the Global Influenza Surveillance and Response System (GISRS)[5]; adoption of the Pandemic Influenza Preparedness (PIP) Framework[6], improved detection and monitoring tools; recommendations on target populations for vaccination; expansion of vaccine production capacity in low-middle-income countries (LMICs), and improved One Health collaborations.

But whereas pandemics may galvanize attention, and consequently resources, seasonal influenza continues to be a cause of substantial recurrent morbidity and mortality, the burden of which is often underestimated. Almost 1/8th of the global population will contract influenza each year[1]. Influenza prevention and control is hampered by seasonal variations in vaccine effectiveness[7, 8, 9] and an annual requirement for seasonal influenza re-vaccination. But in the absence of a 'universal' influenza vaccine that imparts long-lasting immunity, substantially greater control of seasonal influenza and, consequently, pandemic preparedness, could be achieved simply by improving vaccination coverage with existing vaccines. Furthermore, the WHO strategy notes that "influenza serves as an ideal pathogen to build capacities for all major areas of IHR (2005) functionality" and that "influenza programmes can enhance core capacities across the public health spectrum"[1].

To improve seasonal influenza vaccination coverage rates, the notion that seasonal influenza vaccine is ineffective needs to be countered by experts who are best able to interpret outcomes of effectiveness studies. And better communications on the benefits of vaccination need to be directed at the public, specifically vaccination target groups[10]. Given the recurring annual burden of seasonal influenza, governments also need to adequately resource seasonal influenza prevention, according to their national priorities, where influenza control should be seen as a critical investment in pandemic response capability. As noted in

the WHO strategy[1], seasonal influenza vaccination provides cost savings to countries, and can provide secondary benefits such as reducing the burden from non-communicable diseases and anti-microbial resistance.

Since there is no global monitoring system for influenza vaccination coverage, assessing progress towards the WHA or other vaccination coverage targets is problematic. The International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) Influenza Vaccine Supply International Task Force (IVS) developed a survey method in 2008 to assess the global distribution of influenza vaccine doses as a proxy for vaccination coverage rates[11]. This serves as a crude estimate of the capability of countries to achieve seasonal influenza vaccination coverage targets in their elderly populations. The purpose of this paper is to augment the previous analyses of seasonal influenza vaccine uptake with the latest data on seasonal influenza doses distributed in 2016 and 2017. This is turn can help to monitor progress toward prevention goals, and identify where there are weaknesses in strategies and tactics, so as to better inform and strengthen policy-making.

2. Methods

The survey methodology was previously described in Palache[11]. Member companies of the IFPMA IVS (Abbott Biologicals, Adimmune Corporation, Biken, Denka Seiken, GC Pharma, GlaxoSmithKline Biologicals, Hualan Biological, Institute of Ultrapure Biologicals, Kitasato Daiichi Sankyo Vaccine, MedImmune, Saint-Petersburg Scientific Research Institute of Vaccines and Sera, Sanofi Pasteur, Seqirus, Sinovac, and Takeda), who manufacture and supply the vast majority of the world's seasonal influenza vaccines, agreed to provide information on the doses of seasonal influenza vaccine supplied to all WHO Member States during 2016 and 2017. The survey results were confidentially collected and aggregated by the IFPMA Secretariat, in compliance with anti-trust regulations. The resulting anonymized database was then combined with the results of the previous IFPMA IVS surveys (2004–2015). Data were available from a total of 200 countries over the 2004-2017 period. Only aggregate, not individual country data, was available from EU for 2016 and 2017.

The manufacturers covered by the survey are based in 13 countries and represent approximately 90% of all influenza vaccine manufacturers globally[12]. Although there has been an increase in the total number of companies producing influenza vaccines in the last decade, the proportion of vaccines covered by the survey has remained relatively constant, declining by only about 5% (from 95% to 90%) since 2013[13].

In order to assess changes in the distribution of seasonal influenza vaccines we used the following parameters, in each year, for all countries, and then categorized into WHO regions:

- the numbers of countries in which any seasonal influenza vaccine doses were distributed;

- the absolute number of seasonal influenza vaccine doses distributed;
- the annual number of countries globally and in each region with doses distributed per 1,000 population ≥ the number of persons 65 years and older per 1,000 population[14] (the hurdle rate - defined in a previous survey[11] as the number of doses required to reach the estimated elderly population, based on the proportion of the elderly proportion, 15.9%, in developed countries, in 2008)**;**
- the number of doses distributed to each country per 1,000 persons.

To adjust for the population size of each country, we used population data from the United Nations' (UN) statistics database[15].

For each of the above parameters, we conducted the following critical analyses over the entire survey period, between each survey year, and over 3 or 4 year intervals (2004 – 2008, 2009- 2013, and 2014 – 2017):

- the compound annual growth rate (CAGR), using Microsoft Excel, where:

  CAGR = [(rate per 1,000 in 2017 – rate per 1,000 in 2004)$^{1/14}$ -1] x 100;

- a Chi-square test, with 1 degree of freedom, for numbers of countries with any distributed doses and with distributed doses ≥ hurdle rate, using Microsoft Excel 2013;
- a two-sided, paired, T-test, in Microsoft Excel 2013 for absolute and relative numbers of doses.
- a two-sided, T-test for two means of unequal variance in Microsoft Excel 2013, for the absolute and relative numbers of doses at intervals 2004-2008, 2009-2013, and 2014-2017.

Given the high level of skew in the absolute and relative numbers of doses, these data were first log-transformed to normalize the distribution, using the function LN in Microsoft Excel 2013.

As in previous IFPMA IVS surveys[11], we also assessed the correlation between the numbers of doses distributed per 1,000 population and country GNI, globally and in each WHO region, using the regression function in Microsoft Excel 2013.

3. Results

3.1 Numbers of countries in which any seasonal influenza vaccine doses were distributed – Globally, the number of countries where any doses of seasonal influenza vaccine was distributed increased from 111 in 2004 to 134 in 2017 (Supplemental Table 1). Although this represents only a 1.5 % CAGR, the change in number of countries is nevertheless significant (Supplemental Table 2). However, there were 8 fewer countries in 2017 than in 2009 and 2011, the years in which the numbers of countries were at their highest over the survey period, and the numbers have remained relatively constant since the 2009 – 2011 spike.

3.2 Absolute number of seasonal influenza vaccine doses distributed – The total number of doses distributed in 2004 was approximately 262 million and this had risen to about 474 million in 2017, an overall significant 81% increase (Figure 1). However, compared to the peak number of doses distributed in 2014 of 534 million doses, the 2017 total represents a -11% decline. The overall growth in the number of doses distributed has largely been driven by an increase in AM (a significant 138% between 2004 and 2017).

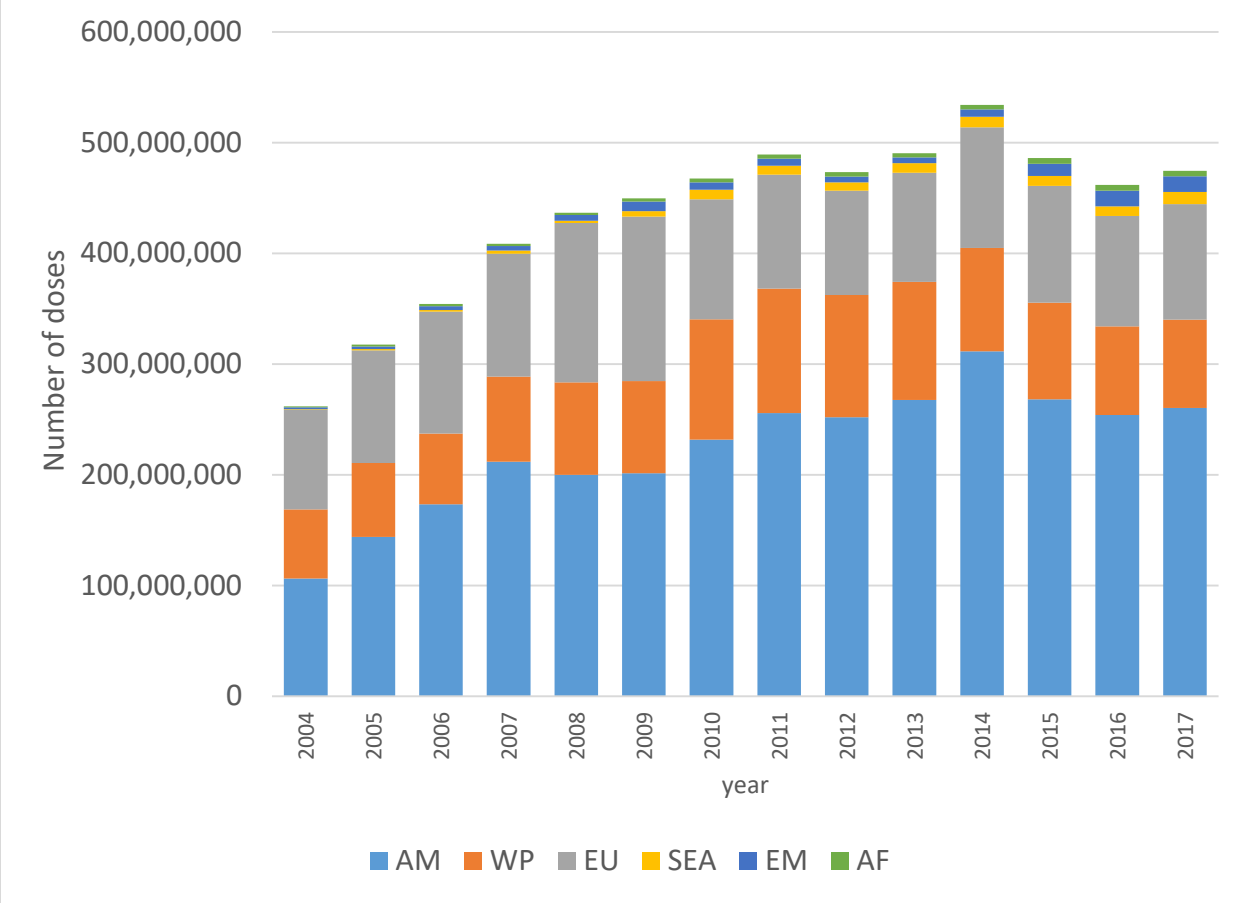

Figure 1. Absolute numbers of seasonal influenza vaccine doses distributed by year and WHO region.

The share of doses distributed to AM has increased from about 41% in 2004 to 55% in 2017, whereas the share for EURO has declined from 34% in 2004 to only 22% in 2017. The share from WP has risen and fallen from year to year, ranging from an all-time high of 24% in 2004 to 17% in 2017. In 2015, three regions, AF, EM, and SEA,

together accounted for just 5% of all doses distributed despite comprising 48.5% of the population of countries surveyed. In 2017, the share from the same three regions increased to only 6%, their populations accounting for 49% of the total.

3.3 Numbers of countries with distributed doses ≥ hurdle rate – Globally, there was only one more country that achieved the hurdle rate in 2017 than in 2004 (Supplemental Table 2). The regions where there was any growth in the proportion of countries achieving the hurdle rate were AM, EM, AF and SEA. In WP and EU there was a decline in proportion of countries achieving the hurdle rates between 2004 and 2017.

3.4 Numbers of doses distributed to each country per 1,000 persons – The AM and EU regions have consistently had higher distribution rates of seasonal influenza vaccine than the global average (Figure 2) (Supplemental Table 2). However, the rates in EU have trended downward since a high in 2009 and there is now a wide spread between rates achieved in AM and EU. Only the AM region has consistently averaged above their hurdle rate. The EU region surpassed the hurdle rate for two years only (2008 and 2009) but in 2016 and 2017 their distribution rates were lower than the rate first achieved in 2005 (Supplemental Table 2). Likewise, the trend in WP is downward with rates in 2016 and 2017 that approximate the rate in 2007. While the global CAGR for doses distributed per 1,000 persons is 3.5, the rate in WP is only 1.3 and 0.7 in EU. The significance of the changes for each parameter are shown in Supplemental Table 3. Although globally there was significant positive change between 2004 and 2007, AM was the only region to have significant positive change for all of the tested parameters. There was no significant change in WP for the same period, and EU was notable for a significant decline in doses per 1,000 persons. All regions except SEA and AF had some significant positive change for the 2004 – 2008 period, but then saw some negative changes for the 2009-2013 period. The EU region had strong significant declines during the latter period. The 2014 – 2017 period saw negative change for all regions except SEA, EM and AF, although these did not achieve significance for the most part.

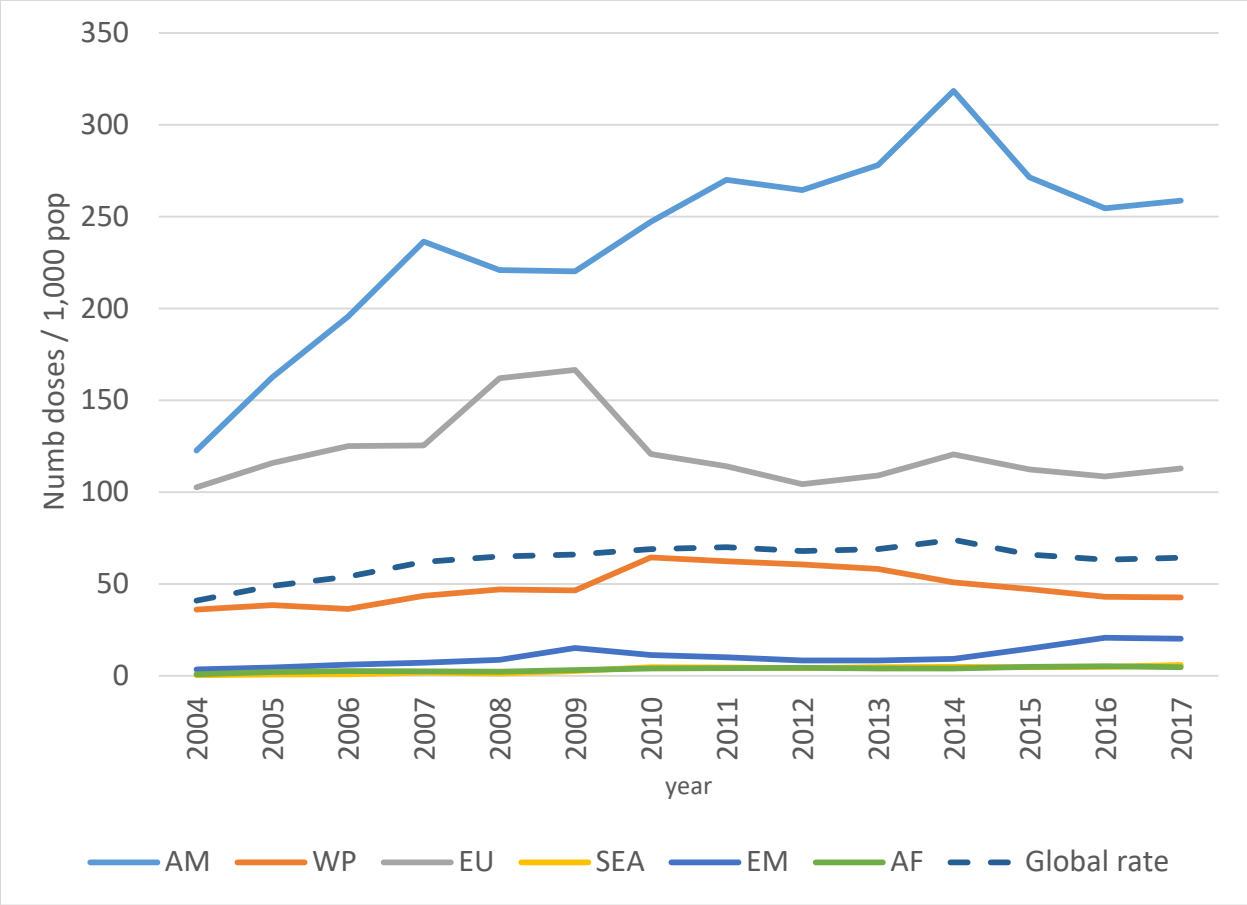

Figure 2. Number of doses of seasonal influenza vaccine distributed per 1,000 persons by year and WHO region.

3.5 Correlation between doses distributed per 1,000 persons and GNI – As in the previous IFPMA IVS surveys, we assessed the correlation between doses per 1,000 population and country GNI for 2016 and 2017 (Table 1). Globally the correlation was weak (r = 0.52, r = 0.56), but in some regions, like WP, a region that combines several small island nations with large continental countries, the correlation was moderate (r = 0.69, r = 0.72). Historically, the correlation had been weakest in the EU region, but we could not confirm this for 2016-2017 because the individual country data was unavailable. The correlations in SEA, EM and AF were higher in 2017 than 2016 but in all cases were weak to moderate.

Table 1. Correlation between numbers of doses distributed per 1,000 population and GNI for 2016 and 2017, using regression in Microsoft Excel.

	2016			2017		
	n	r	significance	n	r	significance
Global	140	0.53	P<0.01	140	0.56	P<0.01
AM	35	0.55	P<0.01	55	0.55	P<0.01
WP	27	0.69	P<0.01	27	0.72	P<0.01
SEA	11	0.21	*not significant*	11	0.60	P<0.05
EM	22	0.38	*not significant*	22	0.45	P<0.05
AF	45	0.37	P<0.01	45	0.53	P<0.01

4. Discussion

The updated 2016-2017 IFPMA influenza vaccine dose distribution survey highlights how little progress has been made in the control of seasonal influenza, and underscores that, under the WHO's Global Action Plan for influenza vaccines (GAP)[16], only in the Americas was a meaningful increase in evidence-based use of seasonal influenza vaccines achieved. Globally there is a clear lack of progress in the control of seasonal influenza, and a clear regression in the numbers of seasonal influenza vaccine doses distributed since 2014 in the three highest-using regions: the Americas (AM), Europe (EU) and the Western Pacific (WP). The number of doses distributed in 2017 is similar to the number distributed in 2012; the number of countries using any seasonal influenza vaccine in 2017 is similar to the number first achieved in 2008; the rate of dose distribution per 1,000 persons was similar to the rate first achieved between 2007 and 2008; there was only one more country achieving the hurdle rate in 2017 than in 2004. Most importantly, there was only a 10% increase in the number of doses distributed per 1,000 persons in EU between 2004 and 2017, compared to a 56% increase at the global level.

Only in AM is there a consistent rate of use above the hurdle rate, which in this study is defined as the number of doses needed to vaccinate 15.9% of the population. However, since the majority of AM countries have introduced pediatric influenza vaccination[17], the hurdle rate only accounts for the elderly population and not the larger total proportion of population for whom vaccination is recommended. Had we adjusted the hurdle rate to include the pediatric population in the AM, the

vaccination coverage rate would have been considerably below the adjusted hurdle rate. Using the hurdle rates as a rough proxy for vaccination coverage in the elderly, Table 2 shows how the coverage rates for influenza contrast with DTP3 vaccination coverage rates in children. The latter are consistently higher in all regions, further highlighting the need for improvements in influenza vaccination performance globally, including in AM, consistent with the WHO GVAP 2030 draft goals for immunization to be delivered across the life-course[18]. Influenza vaccine is the only globally established adult immunization and can serve as the *de facto* platform for administration of other vaccines in adults.

Table 2. Comparison of vaccination coverage rates for influenza, using hurdle rates as a proxy, and WHO reported DTP3 vaccination coverage rates for 2017[19].

	influenza			DPT3
	rate achieved	hurdle rate	coverage %	coverage %
AM	258.7	420.0[i]	61.6	91
WP	42.7	110.4	38.7	97
EU	113.0	160.5	70.4	94
SEA	6.0	61.4	9.8	88
EM	20.3	44.0	46.1	81
AF	4.7	30.7	15.3	72

[i] Adjusted to include population 0 – 19 years and the population 65+ years.

A closer examination of 29 countries that had a 10% or greater decline in distributed doses between 2014 and 2015, shows that declines were in most cases consistent with fluctuations in year to year demand. In both Brazil and Japan there were single year declines of 23 and 15 million doses in 2014-2015 and 2013-2014 respectively. For Brazil, the observed decline was attributable to a shift in the source of vaccine supply to a non-IFPMA supplier, according to the WHO MI4A/V3P vaccine database[20]. However, there was no obvious evidence of shifts of similar size for other countries, which would indicate that the observed declines are in most cases real.

Since the annual burden of influenza-associated disease, hospitalizations and deaths is well recognised and documented[21, 22, 23, 24], and since influenza is known to contribute to social and healthcare costs from NCDs[25, 26, 27, 28, 29], it is hard to explain why there would be a regression in the number of doses of vaccine distributed, and in the number of countries achieving the hurdle rate, particularly in light of an increasingly ageing population in regions like EU[30]. We postulate that despite the thoroughly documented WHO position paper[21], many health care professionals only make modest efforts to implement recommendations for vaccination. The reasons for this, as discussed in detail by Palache 2018[10], include failure to adequately assess and interpret vaccine effectiveness. Counterintuitively, even when vaccine effectiveness is low, large numbers of cases can be prevented as shown in Table 3.

Table 3. Impact of vaccine effectiveness on cases prevented[4].

Numbers of clinical influenza cases prevented by vaccination at an attack rate of 10% Per million population				
Vaccine coverage	Vaccine effectiveness			
	10%	20%	50%	70%
10%	1,000	2,000	5,000	7,000
20%	2,000	4,000	10,000	14,000
50%	5,000	10,000	25,000	35,000
70%	7,000	14,000	35,000	49,000

Salisbury[31] has noted that additional assessments of influenza burden and vaccine effectiveness alone are unlikely to be more persuasive to healthcare providers. Rather, influenza vaccination programs often fail to implement practical measures, such as using near real-time data to monitor program performance[32], assigning leadership within a program, outreach to patients[33], etc, all of which could improve vaccination uptake.

The effectiveness of influenza vaccine programs is also hampered, compared to other vaccination programs, by failing to achieve sufficiently high coverage rates to achieve herd immunity, like for some other diseases[34]. The reasons for low coverage are multiple and include lack of appreciation of disease burden by the public, and challenges for governments in finding fiscal space for influenza vaccines within competing national priorities. To this end, estimates of the impact of influenza vaccination on disease reduction, by year, can be used to make a compelling case to both the public and governments for the value of vaccination[35, 36].

Previous IFPMA IVS survey reports have also highlighted that inadequate reimbursement of influenza vaccination may be a major contributor to underperformance of influenza immunization programs[11]. However, consistent with previous IFPMA IVS surveys, at best there is only a weak to moderate correlation between dose distribution and country income[37, 38, 39], and within each region, there are some higher income countries with lower distribution rates and vice versa.

Poor influenza control is associated with higher rates of anti-microbial resistance (AMR) because of a need to treat secondary bacterial infections or because of inappropriate use and antimicrobials[40]. Influenza vaccination can curtail the prescription of antibiotics[41, 42, 43]. Since AMR has projected socio-economic cost in the $ trillions[44], many governments and international bodies now have efforts to slow AMR, such as in the EU[45].

Similarly, additional efforts are being mobilised to reduce vaccine hesitancy. The WHO promotes the vaccination of healthcare workers both as role models to mitigate vaccine hesitancy, and also to reduce the risk of transmission in the healthcare environment[46]. These, and other efforts, can help to help to reduce the negative trends in seasonal influenza vaccination coverage. But clearly, under GAP, where increasing evidence-based use of seasonal influenza vaccines was an underlying pillar of the action plan, an initial increase in evidence-based use of seasonal influenza vaccine has not been sustained, and uptake of vaccine has remained highly inequitable across regions. The results from this survey suggest that the world is not meaningfully better prepared for a pandemic today than in 2004, as indicated by lack of vaccine development, a current regression in vaccine distribution (and therefore production capabilities), and lack of progress in numbers of countries achieving the hurdle rate. Thus, 33 years after Mostow made his observation, influenza today remains “a preventable disease not being prevented”[47].

Strategies to promote vaccine R&D, viral surveillance, and technology transfers may be important, but they will not reverse the recent negative trend in dose distribution. The WHO Global Influenza strategy 2019-2030 needs to do more than advocate for evidence-based use by deploying tactics and strategies that can preserve and grow the earlier gains in vaccination coverage, in order to alleviate the considerable economic and healthcare burden that now occurs from seasonal influenza[48].

Furthermore, although the 2015 global capacity of approximately 1.5 billion doses[49] is sufficient to meet the 2017 demand, the projected numbers of needed doses to reach the increasing number of elderly in each region with, 50%, 70% or 90% vaccination coverage, will strain the current seasonal vaccine production capacity over the next two decades (Supplemental Table 4). Moreover, there are several additional target populations for seasonal influenza. Ortiz et al[50] reported that of the 115 countries who had seasonal influenza vaccination policies, 28% targeted children, 46% targeted adults with chronic illnesses, 42% targeted pregnant women, and 47% targeted healthcare workers. In sum, the current production capacity may not be sufficient to meet future demand.

Limitations of the study - as previously described[37, 38, 39], the limitations of the IFPMA IVS survey methodology are primarily related to the exclusion of the non-IFPMA manufacturers from the survey, although the vast majority of influenza doses distributed are covered by the survey. As such, we would expect the proportion of vaccine doses from manufacturers that are not covered by the survey, including in large countries like China and Brazil, to be small, and not impactful on the overall outcomes. In the 2016-2017 survey we also did not have access to individual country data for EU, and therefore could not perfume the paired analyses as for the other regions. Also, the survey makes no attempt to examine the impact of vaccination policies and practices on the uptake of vaccine, and so the full context of dose distribution is limited.

For the purpose of comparison between surveys, we utilised persons 65 year or over as the reference group for vaccine coverage. However, we recognize that the 2012 WHO position paper[21] highlights 5 specific target groups for vaccination, and therefore the actual number of doses needed to cover all target groups would be much greater than for the elderly alone. As such, our method underestimates the true coverage gaps.

Despite these limitations, our data is the most comprehensive that exists, and is representative of the current global situation related to global influenza prevention.

5. Conclusion

The current IFPMA IVS survey shows that by several measures, little change in implementation of seasonal influenza vaccination has occurred between 2004 and 2017, outside of AM. The findings underscore the importance and urgency of the WHO strategy, specifically strategic objective 3, to go beyond advocacy and propose to countries concrete strategies and tactics that can improve the use of existing

vaccines. While the benefits of seasonal influenza vaccination are clear and well documented by the WHO, reluctance to implement recommendations and /or poor practices are negating the potential public health benefits. A wholly different attitude and approach to seasonal influenza vaccination is needed. The survey highlights the need for far greater attention in the 2019-2030 strategy on tactics to successfully implement existing policies for seasonal vaccinations in the immediate, pending the availability of future tools. While it is clear that seasonal influenza vaccination programs face challenges that other vaccination programs may not, the 2016-2017 IFPMA IVS survey also highlights that the use of existing solutions is not optimized.

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7. **Supplemental Table 1.** Year to year changes in numbers of using countries and number of doses distributed. CAGR = [(rate per 1,000 in 2017 – rate per 1,000 in 2004)1/14 -1] x 100. The test for significance used for numbers of countries, was the Chi-square test, with 1 degree of freedom. For numbers of doses, a paired 2-sided, student t-test of the natural log of the number of doses (ln(n)) was performed[ii]. Significant changes are denoted by * for P≤0.01, ** for P≤0.05.

	Region (n)		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	CAGR 04-17
n countries and % change from previous year	Global (200)	n	111	111	129	130	133	142	139	142	136	133	133	130	133	134	
		%		0	**16***	1	2	7	-2	2	-4	-2	0	-2	2	1	1.5
	AM (35)	n	23	24	26	27	30	34	31	33	33	31	33	31	32	32	
		%		4	8	4	11	13	-9	6	0	-6	6	-6	3	0	2.6
	WP (33)	n	12	13	15	16	18	18	15	14	16	15	16	16	13	12	
		%	-	8	15	7	13	0	-17	-7	14	-6	7	0	-19	-8	0.0
	EU (53)	n	47	44	44	49	48	50	49	48	47	48	48	47	46	46	
		%		-6	0	11	-2	4	-2	-2	-2	2	0	-2	-2	0	-0.2
	SEA (11)	n	4	5	7	8	7	6	8	9	7	7	7	7	8	9	
		%		25	40	14	-13	-14	33	13	-22	0	0	0	14	13	6.4
	EM (22)	n	15	16	19	17	17	19	17	17	18	18	18	17	18	19	
		%	-	7	19	-11	0	12	-11	0	6	0	0	-6	6	6	1.8
	AF (46)	n	10	9	18	13	13	15	19	21	15	14	11	12	16	16	
		%		-10	**100***	-28	0	15	27	11	-29	-7	-21	9	33	0	3.7
n doses in millions (% change from previous year)	Global	n	261.7	317.5	354.3	408.5	436.5	449.5	467.5	489.1	473.3	490.3	534.0	486.0	461.1	474.0	
		%	-	21	**12***	15	7	**3***	4	5	-3	4	9	-9	-5	7	2.8
	AM	n	106.3	143.9	173.2	211.7	199.8	201.2	231.7	255.6	252.0	267.7	310.9	267.7	252.8	259.3	
		%	-	35	**20***	**22****	-6	1	**15***	**10***	**-1****	6	16	-14	-6	3	7.1
	WP	n	62.3	66.7	63.8	76.9	83.6	83.3	108.6	112.6	110.4	106.4	93.6	87.1	80.0	79.8	
		%	-	7	-4	21	9	0	30	4	-2	-4	-12	-7	-8	0	1.9
	EU	n	90.0	101.7	110.4	111.1	144.2	148.7	108.4	102.8	94.1	98.7	109.7	106.2	99.6	104.2	
		%	-	13	9	**1****	30	3	-27	-5	-8	5	11	-3	-6	5	1.1
	SEA	n	0.5	1.2	1.5	2.9	2.1	4.7	8.6	8.2	7.6	8.7	9.4	9.2	9.5	11.8	
		%	-	148	24	100	-29	127	84	-4	-7	**14****	8	-2	-3	25	28.1

[ii] Not performed for EUR in 2016 and 2017, because individual country data were unavailable, shown in shaded boxes.

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	Region (n)		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	CAGR 04-17
	EM	n	1.8	2.5	3.4	4.0	5.1	8.9	6.7	6.1	5.2	5.2	6.7	10.9	14.0	14.0	
		%	-	35	38	18	27	**76****	-25	-8	-16	0	29	63	29	0	17.0
	AF	n	0.7	1.7	2.1	1.9	1.9	2.6	3.4	3.8	3.9	3.7	3.8	4.8	5.2	4.8	
		%	-	130	**25***	-7	1	36	31	9	**5****	-7	3	29	7	-8	15.7

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8. **Supplemental Table 2.** Year to year changes in number of countries with distributed doses ≥ hurdle rate and number of doses distributed per 1,000 population[iii]. CAGR = [(rate per 1,000 in 2017 – rate per 1,000 in 2004)1/14 -1] x 100. The test for significance used for numbers of countries with distributed doses ≥ hurdle rate was the Chi-square test, with 1 degree of freedom. For numbers of doses per 1,000 population, a paired 2-sided, student t-test of the natural log of the number of doses per 1,000 population (ln(n)) was performed[iv]. Significant changes are denoted by * for P≤0.01, ** for P≤0.05.

	Region (n)		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	CAGR 04-17
n countries ≥ hurdle rates (doses / 1,000 pop) and % change from previous year	Global (200)	hr	72.0	72.6	73.3	73.9	74.4	75.0	75.7	76.8	77.9	79.2	80.6	82.3	84.4	86.6	
		n > hr (%)	40 (20)	41 (21)	41 (24)	47 (24)	50 (25)	54 (27)	43 (22)	47 (24)	49 (25)	45 (23)	41 (21)	43 (22)	46 (23)	41 (21)	0.2
		%	-	3	15	0	6	8	-20	9	4	-8	-9	5	7	-11	
	AM (35)	hr	84.1	85.0	85.9	87.0	88.3	89.7	91.4	93.3	95.4	97.7	100.2	102.9	105.6	108.4	
		n > hr (%)	9 (26)	7 (20)	11 (31)	12 (34)	14 (40)	13 (37)	7 (20)	14 (40)	16 (46)	15 (43)	14 (40)	15 (43)	15 (43)	14 (40)	3.5
		%	-	-22	57	9	17	-7	-46	100*	14	-6	-7	7	0	-7	
	WP (33)	hr	80.2	81.6	83.0	84.3	85.6	87.0	88.7	90.7	92.8	95.2	98.0	101.5	105.7	110.4	
		n > hr (%)	4 (12)	5 (15)	7 (21)	7 (21)	8 (24)	8 (24)	5 (15)	5 (15)	6 (18)	6 (18)	5 (15)	6 (18)	4 (12)	3 (9)	-2.2
		%	-	25	40	0	14	0	-38	0	20	0	-17	20	-33	-25	
	EU (53)	hr	142.3	143.4	144.4	144.8	145.0	145.3	146.1	147.5	149.1	151.1	153.2	155.4	157.9	160.5	
		n > hr (%)	13 (25)	15 (28)	21 (40)	21 (40)	19 (36)	20 (38)	18 (34)	18 (34)	14 (26)	12 (23)	12 (23)	11 (21)	11 (21)	11 (21)	-4.7
		%	-	15	40	0	-10	5	-10	0	-22	-14	0	-8	0	0	
	SEA (11)	hr	48.2	48.8	49.6	50.4	51.2	51.8	52.5	53.5	54.5	55.5	56.7	58.0	59.7	61.4	
		n > hr (%)	0 (0)	0 (0)	0 (0)	1 (9)	0 (0)	1 (9)	2 (18)	2 (18)	1 (9)	1 (9)	1 (9)	1 (9)	1 (9)	1 (9)	0.0[v]
		%	-	0	0	0	-100	0	100	0	-50	0	0	0	0	0	
	EM (22)	hr	40.5	40.6	40.7	40.9	41.0	41.1	41.3	41.5	41.8	42.1	42.5	43.0	43.5	44.0	
		n > hr (%)	1	3	2	2	2	6	2	2	3	3	2	5	7	7	16.1

[iii] Assumes no change in EU from 2015 to 2017, where the number of countries ≥ hurdle rate is not known, shown in shaded boxes.

[iv] Not performed for EU in 2016 and 2017 because paired data unavailable, shown in shaded boxes.

[v] 2007-2017

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	Region (n)		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	CAGR 04-17
			(5)	(14)	(9)	(9)	(9)	(27)	(9)	(9)	(14)	(14)	(9)	(23)	(32)	(32)	
		%	-	200**	-33	0	0	200*	-67	0	50	0	-33	150**	40	0	
	AF	hr	30.3	30.1	30.1	30.2	30.1	30.1	30.0	30.1	30.1	30.2	30.2	30.3	30.5	30.7	
	(46)	n > hr (%)	0 (0)	1 (2)	1 (2)	0 (0)	1 (2)	2 (4)	2 (4)	3 (7)	3 (7)	3 (7)	3 (7)	4 (9)	5 (11)	4 (9)	12.2[vi]
		%	-	0	0	-100	0	100	0	50	0	0	0	33	25	-20	
n doses / 1,000 pop and % change from previous year	Global	hr	72.0	72.6	73.3	73.9	74.4	75.0	75.7	76.8	77.9	79.2	80.6	82.3	84.4	86.6	
		n	41.3	49.6	54.7	62.3	65.8	67.0	69.9	71.2	68.4	70.1	74.9	67.1	63.3	64.3	3.5
		%		**20***	10	**14***	6	**2****	4	2	-4	2	7	-10	-6	2	
	AM	hr	84.1	85.0	85.9	87.0	88.3	89.7	91.4	93.3	95.4	97.7	100.2	102.9	105.6	108.4	
		n	122.7	162.6	195.5	236.4	220.8	220.1	247.2	269.9	264.5	278.1	318.4	271.5	254.5	258.7	5.9
		%	-	33	**20***	**21****	-7	0	**12***	**9***	**-2****	5	14	-15	-6	2	
	WP	hr	80.2	81.6	83.0	84.3	85.6	87.0	88.7	90.7	92.8	95.2	98.0	101.5	105.7	110.4	
		n	36.0	38.6	36.4	43.6	47.0	46.6	64.4	62.3	60.7	58.2	50.9	47.1	43.1	42.7	1.3
		%	-	7	-6	20	**8****	-1	38	-3	-3	-4	-12	-7	-9	-1	
	EU	hr	142.3	143.4	144.4	144.8	145.0	145.3	146.1	147.5	149.1	151.1	153.2	155.4	157.9	160.5	
		n	102.6	115.8	125.1	125.4	162.0	166.6	120.7	114.2	104.3	109.0	120.6	112.4	108.5	113.0	0.7
		%	-	13	8	0	29	3	**-28***	-5	-9	**4****	11	-7	-3	4	
	SEA	hr	48.2	48.8	49.6	50.4	51.2	51.8	52.5	53.5	54.5	55.5	56.7	58.0	59.7	61.4	
		n	0.3	0.7	0.9	1.7	1.2	2.6	4.8	4.5	4.2	4.7	4.9	4.8	4.9	6.0	26.4
		%	-	144	22	97	-30	**124****	82	-5	-8	12	5	-3	2	24	
	EM	hr	40.5	40.6	40.7	40.9	41.0	41.1	41.3	41.5	41.8	42.1	42.5	43.0	43.5	44.0	
		n	3.4	4.6	6.1	7.1	8.8	15.2	11.3	10.1	8.4	8.3	9.3	14.9	20.7	20.3	14.6
		%	-	**33****	34	**15****	24	**73****	-26	-11	-16	-2	12	**59***	39	-2	
	AF	hr	30.3	30.1	30.1	30.2	30.1	30.1	30.0	30.1	30.1	30.2	30.2	30.3	30.5	30.7	
		n	1.0	2.1	2.6	2.4	2.4	3.1	3.9	4.2	4.4	4.0	4.0	5.0	5.2	4.7	12.8
		%		122	**23****	-10	-2	33	26	7	5	-10	**-1****	26	4	-10	

[vi] 2005-2017

9. Supplemental Table 3. Three and four year changes in numbers of countries using any doses, numbers of countries ≥ hurdle rate, number of doses, and number of doses distributed per 1,000 persons[vii]. CAGR = [(rate per 1,000 in 2017 – rate per 1,000 in 2004)1/14 -1] x 100. The test for significance used for numbers of countries, was the Chi-square test, with 1 degree of freedom[viii] . For numbers of doses and doses per 1,000 persons, a two-sided, student t-test for two means of unequal variance of the natural log of the number of doses (ln(n)) was performed[ix] . Significant changes are denoted by * for P≤0.01, ** for P≤0.05.

Region	Change	2004 - 2008	CAGR 04-08	2009 - 2013	CAGR 09-13	2014- 2017	CAGR 14-17	2004 - 2017	CAGR 04-17
Global	n countries any doses (%)	22 (20)*	4.6	-9 (-6)	-1.6	1 (1)	0.3	23 (21)*	1.5
	n using countries ≥ hurdle rate (%)	10 (25)**	5.7	-9 (-17)	-4.5	0 (0)	0	1 (3)*	-1.3
	n million doses (%)	174.8 (67)*	13.6	40.8 (9)**	2.2	-60.0 (-12)	-3.9	212.3 (81)	4.7
	n doses per 1,000 pop (%)	24.5 (59)*	12.3	3.0 (5)*	1.1	-10.6 (-14)	-6.2	23.0 (56)	3.5
AM	n countries any doses (%)	7 (30)*	6.9	-3 (-9)*	-2.3	-1 (-3)	-1.0	9 (39)*	2.6
	n using countries ≥ hurdle rate (%)	5 (56)	11.7	2 (15)	3.6	0 (0)	0.0	5 (56)**	3.5
	n million doses (%)	93.5 (88)*	17.1	66.4 (33)	7.4	-8.3 (-3)	-5.9	146.5 (138)*	7.1
	n doses per 1,000 pop (%)	98.1 (80)*	15.8	57.9 (26)	6.0	-19.4 (-7)	-6.7	136.0 (111)*	5.9
WP	n countries any doses (%)	6 (50)**	10.7	-3 (-17)	-4.5	-4 (-25)	-9.1	0 (0)	0.0

[vii] Assumes no change in numbers of countries ≥ hurdle rate in EU from 2015 to 2017, because data unavailable shown in shaded boxes.
[viii] Not performed for EU for numbers of countries ≥ hurdle rate in 2004-2017 and 2014-2017 because data unavailable shown in shaded boxes.
[ix] Not performed for Global and EU for 2004-2017 and 2014-2017 intervals, because paired data were unavailable shown in shaded boxes.

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Region	Change	2004 - 2008	CAGR 04-08	2009 - 2013	CAGR 09-13	2014- 2017	CAGR 14-17	2004 - 2017	CAGR 04-17
	n using countries ≥ hurdle rate (%)	4 (100)**	18.9	-2 (-25)	-6.9	-2 (-40)	-15.7	-1 (-25)	-2.2
	n million doses (%)	21.2 (34)*	7.6	23.1 (28.0)	6.3	-13.7 (-15)	-5.2	17.5 (28)	1.9
	n doses per 1,000 pop (%)	11.0 (31)*	6.9	11.6 (25)	5.7	-8.2 (-16)	-5.7	6.7 (19)	1.3
EU	n countries any doses (%)	1 (2)	0.5	-2 (-4)	-1.0	-2 (-4)	-1.4	-1 (-2)	-0.2
	n using countries ≥ hurdle rate (%)	6 (46)	10.0	-8 (-40)**	-12.0	-1 (-8)	-2.9	-2 (-15)	-1.3
	n million doses (%)	54.1 (60)	12.5	-50.0 (-34)*	-9.7	-5.5 (-5)	-1.7	14.2 (16)	1.1
	n doses per 1,000 pop (%)	59.4 (58)**	12.1	-57.6 (-35)*	-10.1	-7.6 (-6)	-2.2	10.3 (10)	0.7
SEA	n countries any doses (%)	3 (75)	15.0	1 (17)	3.9	2 (29)	8.7	5 (125)	6.4
	n using countries ≥ hurdle rate (%)	0	-	0	-	0	-	1 (-)	0.0
	n million doses (%)	1.6 (334)	44.3	4.0 (86)	16.9	2.5 (27)	8.2	11.4 (2,404)*	28.1
	n doses per 1,000 pop (%)	0.9 (312)	42.5	2.0 (78)	15.5	1.1 (23)	7.0	5.7 (2,009)	26.4
EM	n countries any doses (%)	2 (13)	3.2	-1 (-5)	-1.3	1 (6)	1.8	4 (27)	1.8
	n using countries ≥ hurdle rate (%)	1(100)	18.9	-3 (-50)	-15.9	5 (133)*	51.8	6 (600)*	16.1
	n million doses (%)	3.2 (179)*	29.2	-3.7 (-42)	-12.7	7.3 (109)**	27.9	12.2 (670)*	17.0
	n doses per 1,000	5.4 (156)*	26.5	-6.9 (-45)	-14.0	11.0 (118)*	29.6	16.8 (490)*	14.6

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Region	Change	2004 - 2008	CAGR 04-08	2009 - 2013	CAGR 09-13	2014- 2017	CAGR 14-17	2004 - 2017	CAGR 04-17
	pop (%)								
AF	n countries any doses (%)	3 (30)	6.8	-1 (-7)	-1.7	5 (45)	13.3	6 (60)**	3.7
	n using countries ≥ hurdle rate (%)	1 (-)	-	1 (50)	10.7	1 (33)	10.1	4 (-)	12.2[x]
	n million doses (%)	1.2 (167)	27.8	1.0 (39)	8.6	1.0 (27)	8.3	4.1 (563)*	15.7
	n doses per 1,000 pop (%)	1.4 (143)	24.9	0.9 (28)	6.3	0.7 (18)	5.6	3.7 (381)	12.8

[x] 2005-2017

10. Supplemental Table 4. Projected number of vaccine doses (in millions) needed for vaccination coverage of 50%, 70%, 90%, and 100% of the elderly in 2020, 2030, and 2040.

	Vaccination coverage level	2020	2030	2040
Global elderly	50%	363.7	498.6	650.1
	70%	509.2	698.1	910.2
	90%	654.7	897.5	1,170.2
	100%	727.5	997.3	1,300.2
Global elderly and AM pediatric	50%	513.1	644.0	790.6
	70%	718.3	901.6	1,106.8
	90%	923.5	1,159.2	1,423.0
	100%	1,026.1	1,288.0	1,581.1
AM elderly	50%	59.4	81.2	100.1
	70%	83.1	113.6	140.2
	90%	106.9	146.1	180.2
	100%	118.8	162.3	200.2
AM elderly and pediatric	50%	209.2	222.4	236.4
	70%	292.8	311.4	330.9
	90%	376.5	400.3	425.5
	100%	418.3	444.8	472.8
WP elderly	50%	119.9	166.5	224.7
	70%	167.8	233.1	314.5
	90%	215.8	299.8	404.4
	100%	239.8	333.1	449.3

	Vaccination coverage level	2020	2030	2040
EU elderly	50%	78.5	95.8	108.5
	70%	109.9	134.1	151.8
	90%	141.3	172.4	195.2
	100%	157.0	191.6	216.9
SEA elderly	50%	67.8	98.9	135.1
	70%	94.9	138.4	189.2
	90%	122.0	178.0	243.2
	100%	135.5	197.7	270.3
EM elderly	50%	17.0	25.9	38.5
	70%	23.8	36.3	53.9
	90%	30.6	46.6	69.4
	100%	34.0	51.8	77.1
AF elderly	50%	17.4	24.8	36.2
	70%	24.3	34.7	50.7
	90%	31.3	44.6	65.2
	100%	34.8	49.6	72.4