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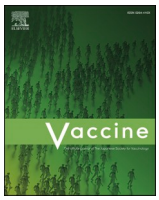

Global production capacity of seasonal and pandemic influenza vaccines in 2023

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ABSTRACT

Introduction: Vaccination is a critical part of the response to an influenza pandemic. Future influenza pandemics will likely leverage existing production processes and manufacturing facilities for seasonal influenza to make pandemic vaccines. Therefore, pandemic influenza vaccine response is heavily dependent on seasonal influenza vaccine production capacity.

Methods: WHO monitors global vaccine production to inform pandemic preparedness by regularly surveying influenza vaccine manufacturers to estimate both seasonal and potential pandemic vaccine production capacity overall and by region, vaccine type, and manufacturing process. The last survey estimates were for 2019; here, we report updated estimates based on data from the 2023 survey and compare to estimates from previous surveys.

Results: Our analysis estimates that annual seasonal influenza vaccine production capacity has remained relatively stable since 2019 at 1.53 billion doses and pandemic vaccine capacity at 4.13 and 8.26 billion doses for moderate and best case scenarios, respectively. Over 80 % of seasonal and pandemic vaccine production capacity relies on embryonated eggs, and inactivated influenza virus vaccines comprise the majority of vaccine supply. There is influenza vaccine manufacturing capacity in all WHO regions, except for the African Region, though influenza vaccine production is concentrated in high and upper-middle income countries. The ability to achieve maximum production capacity could be hindered by access to eggs and other ancillary supplies.

Conclusions: While influenza vaccine production capacity has been sustained since 2019, significant gaps persist in its distribution, especially in low and lower-middle income countries, and most notably in the African region. This imbalance in production could result in unequal access to vaccines in the event of a pandemic. Strengthening local vaccine manufacturing, promoting seasonal vaccination programmes, and investing in research and development of next-generation influenza vaccines or improved production platforms are essential to improve pandemic preparedness, sustain the influenza vaccine market, and enable more robust local responses.

1. Introduction

Vaccination is the primary public health intervention for influenza prevention and control, including for both seasonal and pandemic influenza. Current seasonal vaccines are safe and effective at preventing severe disease and are recommended by the World Health Organization (WHO) for multiple target groups [1]. The WHO Global Influenza Strategy 2019–2030 (GIS) highlights the importance of seasonal vaccination not only for its impact in reducing the burden of seasonal influenza, but also for its role in strengthening pandemic preparedness and response [1,2]. As such, WHO recommends that all countries consider implementing a seasonal influenza vaccination programme [3].

The linkage between seasonal influenza vaccination programmes and pandemic preparedness and response has been documented to build capacity at the operational and programme level [4–6]. In addition, seasonal vaccine production capacity is directly linked to pandemic vaccine production capacity where pandemic influenza vaccines would largely be produced by existing seasonal influenza vaccine manufacturers, using similar technology and facilities. New technologies, especially those used during the COVID-19 pandemic, such as mRNA vaccines may have an important role in future influenza pandemics [7]. Responding to calls for a valuation of their potential and equitable impact from the R&D community and country decision makers, WHO is assessing current and future vaccine supply, market demand, and full

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health and economic impact in a *Full Value of Improved Influenza Vaccine Assessment (FVIVA)* [8–11].

Global demand for seasonal influenza vaccines has increased over time [12,13]. However, it is heavily concentrated in high and upper-middle income countries and in certain regions. In 2022, approximately 760 million doses were procured globally, with 97 % of those vaccines consumed by high and upper-middle income countries and 92 % by countries in the Region of the Americas, European Region, and Western Pacific Regions [14]. Estimates from doses distributed by influenza vaccine manufacturers show a similar level of consumption recently (797 million doses in 2021), which is over triple the amount distributed in 2004 [12]. Seasonal influenza vaccine demand is expected to rise by approximately 10 % over the next decade, with significant opportunities for expanding vaccine use, especially in lower-middle and low income countries [14].

Current seasonal influenza vaccines include inactivated influenza vaccines (IIV), live-attenuated influenza vaccines (LAIV), and recombinant vaccines. Embryonated chicken eggs (egg-based) or cell-culture (cell-based) serve as the substrate for production. While IIV and LAIV are grown and propagated from a physical seed influenza virus in eggs or cells, recombinant vaccines only require genetic information to begin their manufacturing process. Recombinant vaccines currently licensed for influenza use a baculovirus expression vector system in insect cells to express and produce the influenza antigens used in the resulting vaccine.

Seasonal influenza vaccines contain either three (trivalent influenza vaccines, TIV) or four (quadrivalent influenza vaccines, QIV) strains of circulating influenza A and B viruses. The QIV formulation was introduced in 2013, containing two A strains and two B strains versus the TIV formulation with only one B strain. However, in September 2023, WHO recommended that the B/Yamagata lineage antigen should no longer be included in seasonal influenza vaccines, and countries have begun to procure TIV exclusively [15]. Generally, seasonal influenza vaccines are dosed at 15μg of antigen per strain, so TIV and QIV contain 45μg and 60μg of antigen, respectively. A pandemic vaccine is expected to be monovalent (one influenza A strain), though the amount of antigen per dose may vary depending on the immune response to the pandemic vaccine strain and whether adjuvant is used.

The consequences of a future influenza pandemic could be severe. The most well-known influenza pandemic, the 1918 “Spanish Flu”, infected an estimated one- third of the global population and killed up to an estimated 50 million people [16,17]. H5, H7, and H9 viruses have caused sporadic infections and deaths as well as outbreaks in humans [18,19]; highly pathogenic avian influenza (HPAI) viruses from different H5N1 clades are estimated to have a cumulative case fatality over 50 % [20]. As of January 2025, H5N1 viruses have been widely circulating globally in wild and domestic avian and mammalian species, with an unprecedented number of infections from outbreaks in US dairy and poultry farms, highlighting the ever-present risk of the next influenza pandemic.

Recognizing the risk posed by influenza pandemics, the Global Action Plan for Influenza Vaccines (GAP) was launched in 2006 by WHO as a ten-year strategy to increase equitable access to pandemic influenza vaccines. From 2007 to 2019, WHO supported local and regional influenza vaccine production capacity building through the GAP/Technology Transfer Initiative (TTI) programme [21,22]. This programme supported 14 developing country manufacturers in establishing or enhancing of influenza vaccine production capacity between 2007 and 2019. Nine out of the 14 manufacturers were able to produce and obtain approval for a seasonal or pandemic vaccine product through the initiative [21], and several of these manufacturers are still active in vaccine production. WHO remains committed to building local vaccine production capacity - the mRNA Technology Transfer Programme, a joint initiative with Medicines Patent Pool (MPP), is currently helping to establish mRNA vaccine manufacturing capabilities in low- and middle-income countries [23]. In an emergency, such as an influenza pandemic, these capabilities could be leveraged for local capacity. One Programme partner is focusing on developing an H5N1 mRNA influenza vaccine. If successful, this technology would be shared with all 15 partners.

As part of its strategy, GAP had a goal of increasing global production capacity to be able to produce enough vaccine to immunize 70 % of the world’s population with two doses of a pandemic vaccine within six months from the availability of the vaccine virus strain to manufacturers. To measure progress in reaching this goal, WHO regularly conducts surveys of influenza vaccine manufacturers to estimate global vaccine production capacity. Over the course of GAP, global influenza vaccine production capacity tripled, from 500,000 in 2006 to 1.47 billion seasonal vaccine doses in 2015, which could potentially support a monovalent pandemic vaccine production capacity of 6.37 billion doses [24]. The last survey conducted estimated a pandemic vaccine production capacity best case scenario of 8.31 billion doses in 2019 [25].

Recognizing the importance of global coordination in pandemic preparedness, WHO has embedded vaccine production monitoring as one of the six high-level actions within the GIS. It is also a part of the Pandemic Influenza Preparedness (PIP) Framework High Level Implementation Plan III (HLIP III) [26]. The PIP Framework is a partnership among Member States, industry, civil society and other stakeholders to improve the sharing of influenza viruses and access to vaccines and other benefits for pandemic preparedness and response [27]. The HLIP III outlines the strategy for strengthening global pandemic influenza preparedness from 2024 to 2030, with a focus on equitable and sustainable supply of pandemic influenza vaccines and other products.

Separate to production capacity monitoring, in January 2024 WHO published a Global Market Study on Seasonal Influenza Vaccines that reports on actual production, supply and demand, and pricing information for seasonal influenza vaccines [14]. It found that adult formulations of unadjuvanted, standard dose IIV and LAIV (80 % of the market) ranged in median price per dose from US$3.54 (lower-middle income countries, TIV, 2022) to US$ 10.67 (high income countries, QIV, 2022), with tiering of prices across income groups and higher prices documented among QIV versus TIV. Price is unaffected by volume procured, suggesting the current seasonal influenza market operates outside of typical supply-demand dynamics [14].

Here, we provide an update on global influenza vaccine production capacity of facilities as of 2023.

2. Methods

To enable comparability of findings, we replicate the methods of the 2019 survey to update estimates of global influenza vaccine production, stratified by vaccine technology and capacity by region and country income-status.

2.1. Data sources and information gathering

Current influenza vaccine manufacturers were identified using an internal WHO database of manufacturers that had previously reported influenza vaccine production capacity and additional desk review to identify any other manufacturers that may have begun producing influenza vaccines since the last survey in 2019. Manufacturers identified were verified for active influenza vaccine product development through review of their website.

Only established influenza vaccine manufacturers doing full production (must produce bulk antigen) were included in this analysis. “Established” manufacturers were defined as those that had already achieved licensure of influenza vaccines and with a currently functional production facility or with licensed facilities on standby for the production of vaccine in the event of a pandemic (relevant for one manufacturer). Manufacturers with facilities or vaccines still under development are not included in this analysis. Manufacturers with mRNA vaccine candidates in Phase 3 development were contacted for an estimation of their production capacity should their vaccine become licensed, however, we were unable to obtain this information, and they

have been excluded from this analysis. Manufacturers with facilities or vaccines in development [7] will be monitored and included in future surveys if there is a change in the status of their product development and licensure.

We identified 32 established influenza manufacturers and invited them to participate in our survey. We received updated information for 20 manufacturers, however, two of them did not provide updated production capacity estimates. For those manufacturers with incomplete surveys and those that did not reply to the request to participate in this survey, we used publicly available data or information shared with WHO previously [25], for which WHO has permission to use in an aggregated manner and provided that the manufacturer actively produces influenza vaccines as confirmed by their website. The majority of information used to fill data gaps came from the 2019 survey [24,25]; information from 2015 dataset was only used for two manufacturers. These two manufacturers did not respond to the 2019 survey, though they were confirmed to still be active in influenza vaccine production, as per their websites. In using previous information for data gaps, we made the assumption that there were no major changes in the types or amounts of vaccines produced.

Verification of data was done by comparing previously reported information to information gathered in this survey. If any major changes were identified, manufacturers were contacted for confirmation.

2.2. Survey

The survey for 2023 data collection was developed based on questions asked in previous surveys, with minor updates and a few additional questions.

Questions included focused on:

- the types of influenza vaccines being produced (production platform, formulation, etc.)
- country locations of vaccine licensure and production facilities
- an estimate of maximum production capacity if operating at full scale
- pandemic preparedness and capacity (i.e., licensed pre-pandemic vaccines, access to dose sparing adjuvants, and expectations for adequate supplies and filling capacity to meet their maximum capacity in the event of a pandemic).

Survey questions were compiled in a Microsoft Word document and shared with manufacturers via email. Manufacturers were informed that all collected data would be presented in an aggregated manner for the purpose of estimating global production capacity of influenza vaccines.

2.3. Calculation of production capacity

Manufacturers were asked to provide estimates of maximum vaccine production capacity in doses, if operating at full scale. Although more than one dose of a vaccine may be needed for an appropriate level of protection in a pandemic, we report total doses able to be produced. In a best case scenario, we assume that the same amount of antigen used for each seasonal strain would be sufficient for a monovalent pandemic vaccine and that the vaccine yield from the pandemic virus strain would be similar to that from seasonal viruses. A moderate case scenario assumes that twice as much antigen would be needed for an adequate immune response.

Manufacturers were asked to provide production capacity estimates for monovalent, trivalent, or quadrivalent vaccine production. It should be noted that these estimates are not an estimate of actual production; they represent the maximum number of vaccine doses that could be produced in 12 months if facilities were operating at full-scale for a given formulation. A flow chart of the information collected and how it was processed is available in Fig. 1. If an estimate for monovalent vaccine production was not provided, the TIV or QIV production capacity was multiplied by three (TIV) or by four (QIV), depending on which estimate was provided. If production capacity estimates for both TIV and QIV, but not monovalent vaccines were provided, the TIV estimate was used to calculate monovalent vaccine production capacity. If only monovalent production capacity was given, this was divided by three for TIV capacity, unless the manufacturer noted that they do not produce seasonal influenza vaccines. The decision to use TIV is based on the current WHO recommendation for the TIV formulation, however, estimation of monovalent capacity from TIV versus QIV results in a more conservative monovalent estimate.

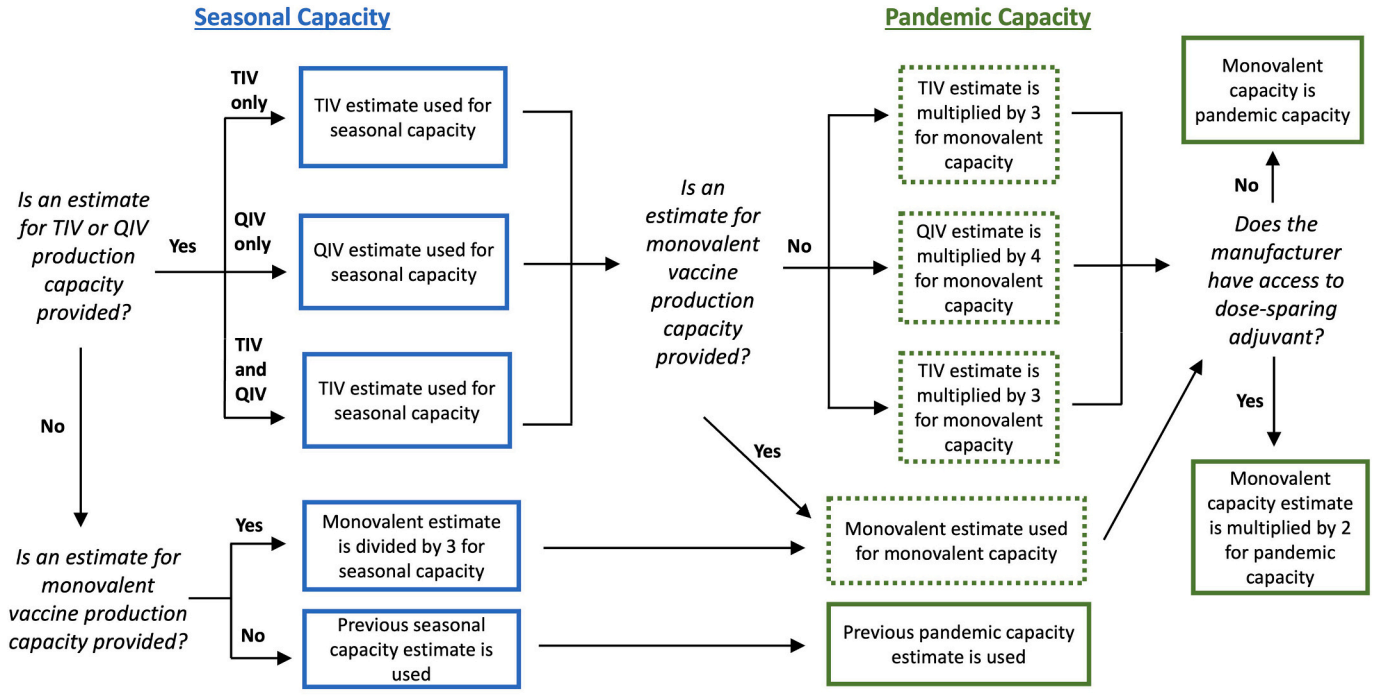

Fig. 1. Decision tree on calculating seasonal or pandemic influenza vaccine production capacity from manufacturer vaccine production capacity estimates.

Global seasonal influenza vaccine production capacity was calculated as the sum of the TIV or QIV production capacity estimate from each manufacturer. If a manufacturer provided both TIV and QIV estimates, the TIV estimate was used as the seasonal vaccine production capacity estimate for that manufacturer.

Fig. 1 provides an overview of how seasonal and pandemic vaccine capacity was calculated for each manufacturer.

Global pandemic vaccine production capacity is derived from the monovalent vaccine production estimates. A manufacturer's pandemic vaccine production capacity is their monovalent vaccine production capacity, unless they indicated they had access to dose-sparing adjuvants. Some adjuvants have been shown to have dose-sparing effects in inactivated and recombinant influenza vaccines [28–33], allowing for an adequate immune response with an antigen dose half or a quarter (7.5 or 3.75μg of HA) of what is included per strain in current seasonal vaccines. As such, we factored usage of squalene-based adjuvants MF59 and AS03 into our pandemic vaccine production capacity estimates, as described previously [25]. If a manufacturer indicated they had access to the dose-sparing adjuvants MF59 or AS03, their monovalent vaccine production capacity estimate was doubled for their final pandemic vaccine production capacity estimate, based on the assumption that use of dose-sparing adjuvant would allow for half as much antigen to be used per dose.

Global pandemic production capacity was calculated for best case and moderate case scenarios. Best case scenario was calculated as the total pandemic influenza vaccine production capacity from each manufacturer. As the moderate case scenario assumes that twice as much antigen is needed for a pandemic vaccine, this estimate was calculated by dividing the best case scenario estimate by two.

2.4. Assumptions used in vaccine production capacity calculations

In a pandemic, many factors could impact vaccine production capacity, such as timing and ease of the transition from seasonal to pandemic vaccine production, which is commonly referred to as the "switch". Key factors include pandemic influenza vaccine strain growth dynamics and yield, egg and other vaccine supply availability, and operational capacity of manufacturing facilities. As such, several assumptions were made in our calculations, using the same as those that were described previously [25], and have been described again in Box 1.

Box 1
Assumptions used in vaccine production capacity calculations

- Manufacturers would not be in the middle of seasonal vaccine production and could "switch" immediately to pandemic vaccine production once the pandemic virus sequence or candidate vaccine virus (CVV) becomes available.
- The pandemic influenza vaccine strain would grow similarly well in eggs and cells as seasonal strains. This was true for H1N1 but may not be for other subtypes [34].
- In a pandemic scenario, there will be an adequate supply of eggs, with egg-laying poultry unaffected by the pandemic or other disruptions. Manufacturers would have access to eggs even off-season, despite not typically ordering them during this time.
- All production steps would proceed without delays. Since influenza vaccine production is time-intensive and interconnected, any delay in one step could affect overall timelines.
- Manufacturers would have enough filling lines to package the vaccine into vials or syringes, allowing them to meet full production capacity.
- Adequate workforce protection measures would be in place to ensure that production continues uninterrupted.
- There would be a sufficient and timely supply of necessary materials—such as vials, syringes, and functional transport networks—to package and deliver the vaccine.
- Adjuvants like MF59 and AS03 would half the amount of antigen needed per dose for an appropriate immune response, thereby doubling the production capacity for manufacturers with access to these adjuvants.

Table 1
Established influenza vaccine manufacturers.

Manufacturer	Bulk vaccine production sites (countries)	Vaccine type
Abbott Biologicals B.V	The Netherlands	IIV, egg-based
AdImmune Corporation	China	IIV, egg-based
AstraZeneca PLC	United Kingdom	LAIV, egg-based
Bayerpaul Group	Iran (Islamic Republic of)	IIV, egg-based
BIKEN Co., Ltd	Japan	IIV, egg-based
Changchun BCHT Biotechnology Co.*	China	LAIV, egg-based
China National Biotec Group (CNBG)	China (2 facilities)	IIV, egg-based
CPL Biologicals Pvt. Ltd	India	Recombinant VLP, cell-based
CSL Seqirus	Australia, the United Kingdom, the USA	IIV, egg-based and cell-based
Daiichi Sankyo Co., Ltd.	Japan	IIV, egg-based for seasonal, cell-based for pandemic
Dalian Aleph Biomedical Co., Ltd.	China	IIV, egg-based
Denka Seiken Co., Ltd.	Japan	IIV, egg-based
FLUART Innovative Vaccines Kft	Hungary	IIV, egg-based
FORT LLC	Russian Federation	IIV, egg-based
GC Biopharma corp.*	Republic of Korea	IIV, egg-based
GlaxoSmithKline (GSK)	Canada, Germany	IIV, egg-based
Hualan Biological Engineering Inc.	China	IIV, egg-based
IL-YANG PHARM., CO. LTD.	Republic of Korea	IIV, egg-based
Instituto Butantan*	Brazil	IIV, egg-based
Institute of Vaccines and Medical Biologicals (IVAC)*	Viet Nam	IIV, egg-based
Jiangsu GDK Biotechnology Co., Ltd.	China	IIV, egg-based
KM Biologics Co., Ltd.	Japan	IIV, egg-based for seasonal, cell-based for pandemic
Mechnikov Institute	Nicaragua	IIV, egg-based
NPO Microgen JSC	Russian Federation	IIV, egg-based
Saint-Petersburg Scientific Research Institute of Vaccines and Sera (SPbNIIVS)	Russian Federation	IIV, egg-based
Sanofi Pasteur	China, France, Japan, Mexico, the USA	IIV, egg-based and recombinant, cell-based
Serum Institute of India Pvt. Ltd.*	India	LAIV, egg-based
Sinovac Biotech Ltd.	China (2 facilities)	IIV, egg-based
SK Bioscience Co., Ltd.	Republic of Korea	IIV, cell-based
Takeda Pharmaceutical Company Limited	Japan	Approved facility for cell-based pandemic IIV
Torlak Institute of Virology, Vaccines and Sera*	Serbia	IIV, egg-based
Zydus Lifesciences Ltd.	India	IIV, egg based

* GAP/TTI Programme grantee.

3. Results

The results of the 2023 WHO Influenza Vaccine Production Capacity Survey are presented in aggregate to maintain the confidentiality of individual manufacturers.

3.1. Production landscape

This analysis identified 32 national and multinational vaccine manufacturers with a total of 41 influenza vaccine bulk manufacturing facilities in 19 different countries. This represents an additional manufacturer, country with production capacity, and manufacturing site to

the list since 2019, due to the addition of Torlak Institute of Virology, Vaccines, and Sera (Serbia) as an established influenza vaccine manufacturer. The list of established influenza vaccine manufacturers, as of 2023 information, is summarized in Table 1.

There is influenza vaccine production capacity in almost all regions of the world, with the exception of the African Region (Table 2 and Fig. 2). The Western Pacific Region has the largest number of influenza vaccine production facilities, followed by the European Region. However, this does not necessarily correlate with the quantity of doses able to be produced, as capacity at different production facilities vary widely. This is demonstrated by the breakdown of production capacity by country income status (Table 3) – while the number of manufacturing facilities are similar between high income and upper-middle income status country groupings (19 in high income countries, 17 in upper-middle income countries), the share of global influenza vaccine production capacity in high income countries (68.88 % of seasonal capacity; 79.76 % of pandemic capacity) is over double and quadruple that from upper-middle income countries (29.57 % of seasonal capacity; 19.72 % of pandemic capacity), with the small remainder in lower-middle income countries. There are no influenza vaccine manufacturing facilities in low income countries, and influenza vaccine production from lower-middle income countries represents only 1.55 % and 0.53 % of the global total for seasonal and pandemic production, respectively. Despite low- and middle- income countries accounting for 82 % of the world's population in 2023 [35], their contribution to seasonal and pandemic vaccine production is minimal when compared to high income countries which represent only 18 % of the world's population. The distribution of global capacity by country income status has not appreciably changed since 2019, remaining at nearly the same numbers [25].

3.2. Production capacities

Estimated influenza vaccine production capacity is described below and summarized in Tables 4 and 5.

Seasonal influenza vaccine production capacity.

Global seasonal influenza vaccine production capacity in 2023 was estimated as 1.53 billion doses able to be produced in a 12-month period. Approximately 14 % of that capacity is produced by the six GAP/TTI grantees as noted in Table 1.

Overall, seasonal vaccine production capacity has been relatively stable since 2011 (Fig. 3), with this current estimate representing a slight increase in seasonal vaccine production capacity since 2019 (a 3.7 % increase from the previous survey's estimate of 1.48 billion doses of seasonal vaccine [25]).

Almost 90 % of seasonal influenza vaccine production capacity uses egg-based production technology, which includes IIV and LAIV products. Approximately 90 % of the egg-based production capacity is IIV. Eleven percent of seasonal influenza vaccine production is cell-based, including IIV grown in mammalian cells or recombinant vaccines using insect cells. CPL Biologicals Pvt. Ltd. and Sanofi Pasteur both produce influenza vaccines from recombinant technology using insect cells; the former produces Cadiflu-S, a virus-like particle vaccine containing the haemagglutinin (HA), neuraminidase (NA) and matrix 1 (M1) proteins, and the latter produces Flublok, a recombinant HA protein vaccine. There are three LAIV manufacturers: AstraZeneca PLC, Changchun BCHT Biotechnology Co., and Serum Institute of India Pvt. Ltd. (Table 1). The distribution of influenza vaccine manufacturers is generally spread equally between those producing only TIV, only QIV, or both TIV and QIV.

Table 2
Number of active influenza vaccine production facilities by WHO region.

WHO Region	Number of production facilities (change from 2019)
African Region	0 (no change)
Region of the Americas	6 (−1)
Eastern Mediterranean Region	1 (no change)
European Region	10 (+1)
South-East Asia Region	3 (no change)
Western Pacific Region	21 (+1)

3.3. Pandemic influenza vaccine production capacity

We calculated global pandemic influenza vaccine production capacity to be an estimated 8.26 billion doses of monovalent vaccine able to be produced in a 12-month period for the best case scenario. If twice as much antigen was needed for appropriate protection, the moderate case scenario estimates that 4.13 billion doses of vaccine could be produced in the same time frame. These estimates factor in usage of adjuvant from the four manufacturers that indicated they had access to dose-sparing adjuvant. Pandemic production capacity from the six GAP/TTI grantees represents 6.65 % of the overall global estimate.

Global pandemic influenza vaccine production capacity for 2019 was estimated as 8.31 billion doses, best case scenario, and 4.15 billion doses, moderate case scenario [25], which at that time represented an increase of nearly 2 billion doses since 2015. This level of production capacity has been sustained, as the 2023 estimates have not appreciably changed since 2019. (Fig. 4, Table 4).

About 84 % of pandemic vaccines would be produced in chicken eggs, with the remaining 16 % produced in cells. Over 85 % of the egg-based pandemic production capacity would be IIV. The proportions of pandemic vaccine types and substrate differ from those from seasonal vaccine production capacity because:

- Two manufacturers indicated that they would use cell-based technology in a pandemic as opposed to their seasonal egg-based production,
- One cell-based vaccine manufacturer only produces pandemic vaccines and therefore was not included in the seasonal production capacity estimates, and
- Some manufacturers with cell-based seasonal production produce QIV which is quadrupled in the monovalent and pandemic production estimate.

Access to and the ability to procure eggs and ancillary supplies in an off-season could affect pandemic vaccine production capacity, as could filling line capacity, if manufacturers do not have sufficient filling lines available to fill their vaccine into vials or syringes to meet their maximum capacity. Fig. 5 summarizes information provided by manufacturers on these potential limiting factors, using responses from 2023 data collection and supplementing with data on file from previous WHO surveys. 53 % of manufacturers expect to have adequate access to eggs and ancillary supplies to achieve maximum vaccine production; 44 % have standard operating procedures (SOPs) in place to source eggs or ancillary supplies in an off-season in the event of a pandemic. While access to eggs may not be an issue for some manufacturers, a few manufacturers indicated that access to other raw materials and supplies could be a limiting factor. The majority of manufacturers reported that filling lines should not be a limiting factor in global pandemic influenza vaccine production, with 75 % of them (includes data from previous surveys) indicating that they would have sufficient access to filling lines to ensure maximum production.

The first doses of a pandemic vaccine could be available within 4–6 months from start of production, based on vaccine production timelines from the 2009 H1N1 influenza pandemic and current timeline estimates. Vaccine production would likely be equally spread out during a 12-month period, after initial lead time and regulatory processes, as manufacturers that provided the breakdown of vaccine production estimates over 3-month increments indicated as such. Still, scaling up to maximum capacity, would have an initial lead time, and there could be some differences in production timelines based on type of vaccines. IIV could be

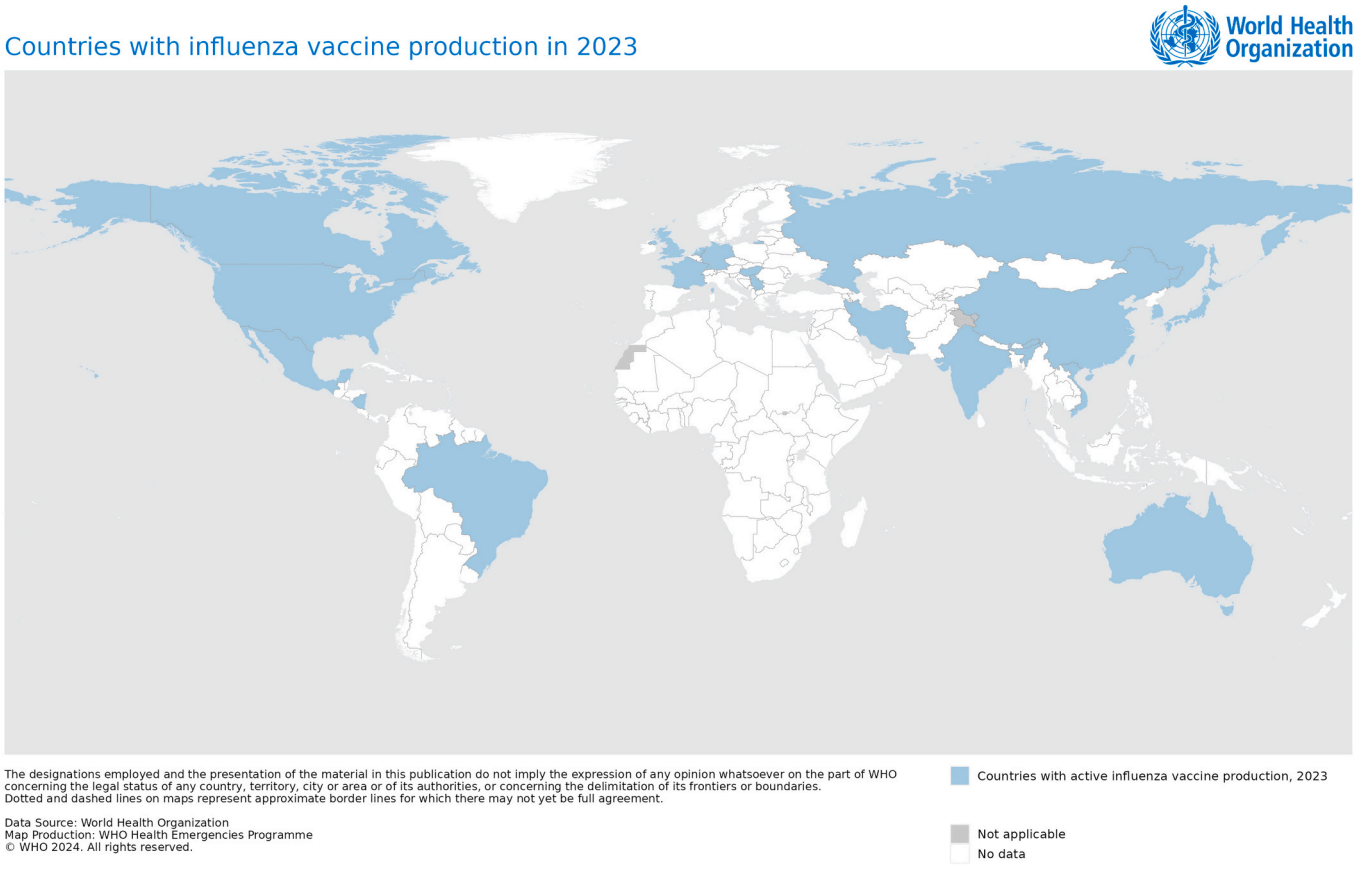

Fig. 2. Countries with influenza vaccine production, 2023. Only countries with influenza vaccine manufacturing facilities doing full production (must produce bulk antigen) are included in this map. Additional countries have facilities that conduct fill/finish operations or may have production facilities in development, however, they have been excluded from this map.

Table 3
Number of active influenza vaccine production facilities by income status of country of production* **.

Income Status	Number of production facilities (change from 2019)	% of global production capacity (seasonal) (change from 2019)	% of global production capacity (pandemic) (change from 2019)	% of world population*
Low income	0 (no change)	0 %	0 %	9.04 %
Lower-middle income	5 (no change)	1.55 % (−0.11)	0.53 % (−0.01)	38.26 %
Upper-middle income	17 (+2)	29.57 % (+0.65)	19.72 % (+0.64)	35.15 %
High income	19 (−1)	68.88 % (−0.54)	79.76 % (−0.63)	17.55 %

*World Bank Classification and data 2023 [35].
** Note that the change in percentages from 2019 was calculated using the raw data set with numbers rounded to 2 decimal places for comparison as the 2019 publication rounded to the nearest whole number.

produced in 23–24 weeks, from the time that a pandemic vaccine strain recommendation is made and the CVV or genetic sequence becomes available to deployment of the pandemic vaccine product; LAIV could be produced in a slightly shorter time frame, 21 weeks [36]. Recombinant vaccines could potentially be produced more quickly, as they do not require physical CVVs to begin production and purified antigen can be produced in 38 days [37]. However, this advantage upstream may not reduce overall manufacturing time to finished recombinant vaccine product available for deployment if the later stages in vaccine production (testing, scale-up, licensure) are not streamlined and able to occur soon after. mRNA vaccines could be produced even more quickly than current influenza vaccines, however, these vaccines are not yet available for influenza. Even though they may be quicker to produce, the clinical evaluation of vaccines using mRNA or other novel recombinant technology may take longer during a pandemic than traditional IIV and LAIV that have a long history of safety and efficacy.

These timeline estimates are impacted by the availability of facility staff, operations, supplies, equipment, raw materials and supply chain dynamics in a pandemic. It also assumes that manufacturers would not be in the middle of seasonal vaccine production and could switch immediately to pandemic vaccine production; given the timelines for seasonal influenza vaccine production, this window is limited, especially for those manufacturers that produce both Northern and Southern Hemisphere formulations ($n = 13$).

4. Discussion

Understanding the global influenza vaccine production capacity is important for both seasonal and pandemic influenza preparedness. It provides critical information on the number of potential doses,

Table 4
Summary of estimated production capacities in 2023*

Breakdown of production capacities	Seasonal Influenza (change from 2019)	Pandemic Influenza (change from 2019)
Total annual production capacity		
Seasonal influenza vaccines	1.53 billion doses (+55 million)	
Pandemic influenza vaccines (moderate case)		4.13 billion doses (−22 million)
Pandemic influenza vaccines (best case)		8.26 billion doses (−44 million)
By substrate		
Embryonated eggs	88.77 % (+4.30)	83.97 % (+4.94)
Cell culture	11.23 % (−4.30)	16.03 % (−4.94)

* Note that the change from 2019 was calculated using the raw data set with exact estimates for capacity in doses and numbers rounded to two decimal places for share by substrate.

Table 5
Summary of estimated production capacities in 2023 from GAP/TTI grantees.

Total annual production capacity from GAP/TTI grantees	Doses	% of global capacity
Seasonal influenza vaccines	211,260,000	13.78 %
Pandemic influenza vaccines (moderate case)	274,763,000	6.65 %
Pandemic influenza vaccines (best case)	549,526,000	6.65 %

distribution, and type of vaccine production anticipated during a pandemic, which guides WHO's activities to support equitable access to vaccines and capacity building for pandemic preparedness and response.

This analysis, which includes information from 2023 and previous data shared with WHO for this purpose, estimates that 1.53 billion doses of seasonal vaccine can be produced on an annual basis if manufacturers are operating at full scale. This capacity translates to an estimated 4.13 (moderate case) to 8.26 (best case) billon doses of pandemic vaccine that could be produced within 12 months. The best case scenario could theoretically vaccinate the entire global population in 2023 (8.02 billion [35]) with one vaccine dose, though it is likely that two doses would be required for sufficient protection, thereby reducing potential vaccination coverage to half the global population. It is also likely that initial vaccine distribution would be inequitable between high income countries and low- and middle- income countries, based on the global distribution of vaccine production capacity and timelines and patterns from previous pandemics. Approximately 14 % and 7 % of seasonal and pandemic production capacity, respectively, comes from GAP/TTI programme grantees. Pandemic influenza vaccines could be produced by 32 established national and multinational manufacturers. The majority of pandemic vaccines would be egg-based (84 %), with IIV comprising over 85 % of this egg-based supply. There is influenza vaccine production capacity in all regions of the world, except for the African Region, though capacity continues to be almost exclusively concentrated in upper-middle and high income countries. Almost 80 % of pandemic vaccine capacity is based in high income countries, and 20 % in upper-middle income countries, with a very small fraction in lower-middle income countries; these numbers remain largely the same since 2019. In addition to data gathered from surveys, the ability to achieve maximum production capacity could be hindered by access to eggs, ancillary supplies, availability of workforce, and global supply chains.

The results of this survey represent our best efforts to estimate global vaccine production capacity given limitations in information available or provided by manufacturers and assumptions made in our calculations and conditions under which maximum production capacity could be met. It is possible that we have not captured all influenza vaccine manufacturers, which might underestimate production capacity in certain regions or among low and lower-middle income countries. However, we do not expect that potential omissions would largely affect overall global capacity, as manufacturers with the largest shares of the market are included in this analysis, which aligns with other landscapes and studies.

Both seasonal and pandemic influenza vaccine production capacity has remained relatively the same since the last survey in 2019, with a slight increase (3.7 %) in seasonal capacity and less than a percent decrease in pandemic capacity. However, since 2013, manufacturers have been switching their production to or adding the QIV formulation to their seasonal production, which typically requires 33 % more antigen per dose than TIV to account for the additional B strain. Increases in QIV manufacturing could translate into increased monovalent vaccine production capacity, despite the stabilized seasonal production capacity. Our calculations do not factor in the impact of changes in QIV production, so our calculated pandemic production capacity may be an underestimate.

Market dynamics may also affect vaccine production capacity over time and may influence facility operations. Seasonal production capacity can fluctuate based on seasonal vaccine demand, as manufacturers procure supplies and plan production based on current demand. Manufacturers can only produce based on the supplies and operational capacity at a point in time, which affects what maximum production

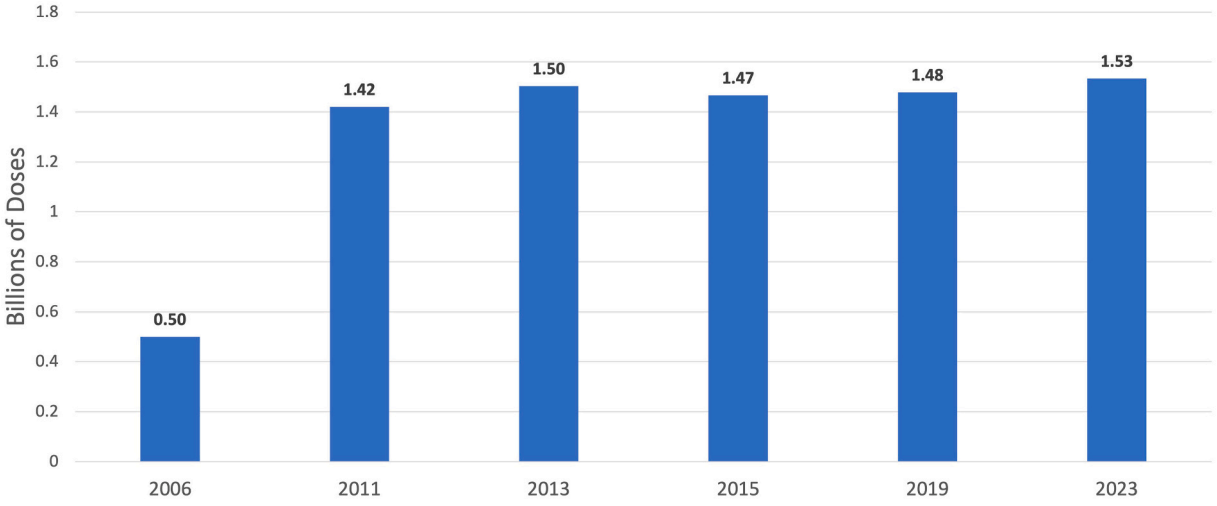

Fig. 3. Estimated total annual seasonal production capacity over time (since 2006). The estimated number of seasonal influenza vaccine doses able to be produced in 12 months if manufacturers were operating at full-scale, displayed over time.

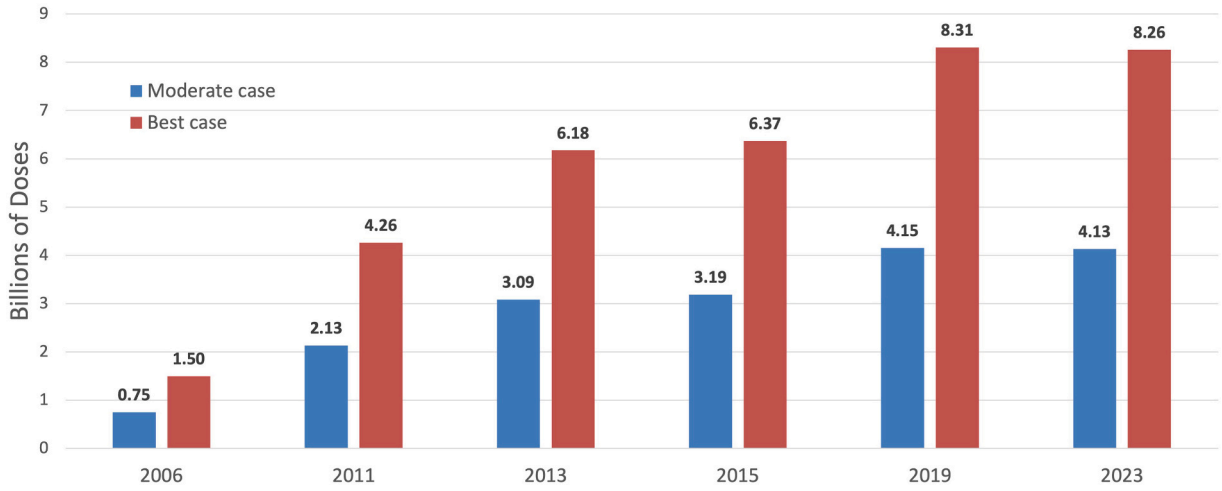

Fig. 4. Estimated potential annual pandemic production capacity over time (since 2006). The estimated number of pandemic influenza vaccine doses able to be produced in 12 months if manufacturers were operating at full-scale, displayed for best case and moderate case scenarios over time. Best case scenario–manufacturers would be able to operate at full scale with no limitations on supplies/reagents, the pandemic strain would grow equally well in eggs/cells as seasonal strains and the same amount of antigen as normally used for each seasonal strain would be enough to elicit an adequate immune response. Moderate case scenario–manufacturers would be able to operate at full scale with no limitations on supplies/reagents, the pandemic strain would grow equally well in eggs/cells, however twice the amount of antigen as per each strain of seasonal would be required to elicit an adequate immune response.

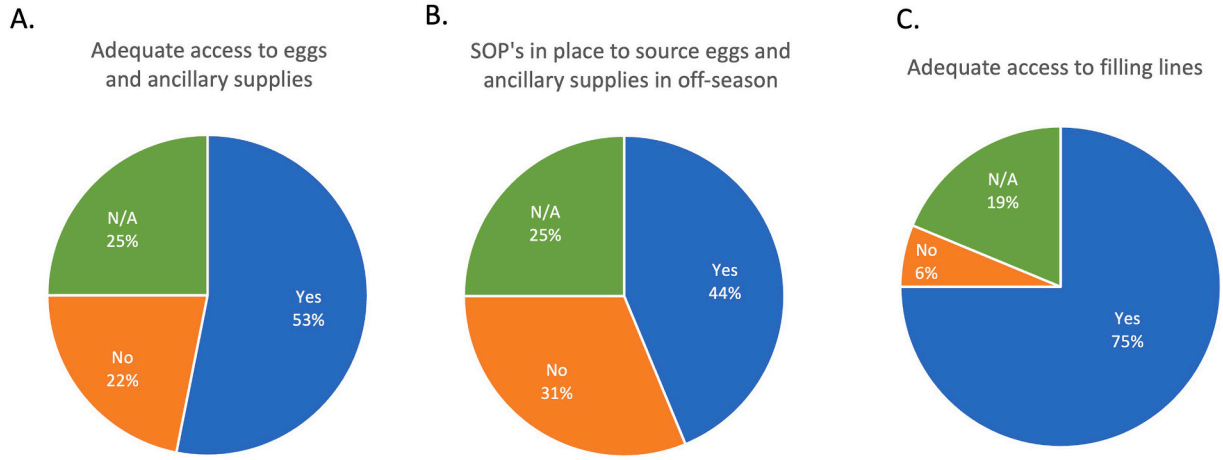

Fig. 5. Pandemic vaccine readiness of influenza vaccine manufacturers. The percentage of manufacturers that answered yes, no, or not applicable (N/A) to questions related to having (A) adequate access to eggs and ancillary supplies, (B) standard operating protocols (SOPs) in place to source eggs and ancillary supplies in the off-season, and (C) adequate access to fillings lines to achieve maximum production capacity. The percentages of each answer are inclusive of information gathered in the 2023 survey and previous surveys.

capacity would be estimated at that same point in time. Demand for influenza vaccines increased considerably between 2020 and 2022 in response to the COVID-19 pandemic, as evidenced by doses distributed and procured globally [12,14]. However, in the US, which represents a large proportion of the global market, vaccination rates and doses distributed have decreased in recent years [38,39], dropping to below pre-pandemic levels for the 2023–2024 season. During this season, approximately 10 % fewer influenza vaccine doses were distributed than from what had been distributed in 2019–2020 and in the prior 2022–2023 and 2021–2022 seasons [39]. While not as large, there was a 3 % decline globally in the volumes of seasonal influenza vaccines purchased between 2021 and 2022 [40]. WHO is continuing to monitor trends in the global seasonal influenza vaccine market. If a trend in decreased demand for influenza vaccines persists, global production capacity could be impacted.

The majority of influenza vaccine production is based on the IIV platform and uses embryonated chicken eggs as the substrate for virus growth and subsequent antigen production. Egg-based production of IIV is relatively low cost and its manufacturing process and regulatory approval pathway are well established [22]. However, influenza vaccine viruses grown in eggs could develop mutations through their adaptation to and growth in this substrate, which could reduce vaccine effectiveness [41]. Also, access to and the availability of eggs impacts egg-based vaccine production. While most manufacturers expected to have sufficient access to eggs or do not rely on eggs for production (cell-based vaccines), approximately half do not currently have SOPs in place to source eggs or ancillary supplies if a pandemic were to occur during the off-season. External factors could negate manufacturer preparedness, for instance if outbreaks of avian influenza in poultry require flock culling and reduce egg supply. This impact could be greater in the event of an influenza pandemic if that virus is also circulating in poultry. Given limitations with egg-based vaccines, the United States National Influenza Vaccine Modernization Strategy 2020–2030 specifically promotes development of non-egg-based influenza vaccines to improve availability and effectiveness of seasonal and pandemic vaccines [42]. Similarly, the majority of vaccines in clinical development for zoonotic

influenza (H5 and H7 subtypes) use non-egg based production technology (Taaffe et al., unpublished data, 2024).

Because of the risks with egg-based production, several manufacturers have indicated their intention to use cell-based vaccine production during a pandemic, and other manufacturers produce cell-based seasonal vaccines, including recombinant vaccines. Cell-based vaccines have the potential to be faster to scale-up than egg-based, and recombinant vaccines may have an upstream advantage in that antigen production may be able to start sooner, as soon as the genetic sequences of the recommended antigen become available. Still, cell-based production capacity represents only 16 % of global pandemic vaccine production capacity, and there could be clinical and regulatory hurdles for recombinant vaccines with the switch to and use for a pandemic vaccine. Establishing clear regulatory pathways for licensing new pandemic vaccines is essential during the inter-pandemic period. This includes both converting existing seasonal vaccines to pandemic vaccines through strain changes and licensing novel vaccines in development, ensuring preparedness before a widespread and urgent need arises.

Sourcing other supplies during a pandemic could also impact production capacity during a pandemic, as it was a documented barrier to vaccine production during the COVID-19 pandemic [43]. Beyond eggs, several manufacturers indicated that sourcing other raw materials and packaging or delivery devices could hinder reaching their maximum capacity. While filling lines to fill and finish packaging of vaccine products is not anticipated to be a limiting factor for most manufacturers, for those that identified this as a potential issue, the ability to use different facilities for additional fill/finish capacity in an emergency should be explored.

Only four manufacturers have access to adjuvants that have been shown to allow for dose-sparing and improve immunogenicity in influenza vaccines. Given their potential for increasing production capacity and improving immunogenicity of pandemic vaccines, expanding access to adjuvants should be a priority action for pandemic preparedness and response. Initiatives such as the Vaccine Formulation Institute, which aims to provide adjuvants and related research, including technology transfer and training, to the entire vaccine community, with a focus on LMICs, are crucial for this effort [44]. However, before using pandemic vaccine products that include adjuvants in new or existing strain formulations, these adjuvanted products would first require clinical evaluation. It would be prudent to conduct such evaluations before a pandemic emergency.

The distribution of production capacity could influence vaccine access in a pandemic. The lack of local production of influenza vaccines could potentially put African and/or low and lower-middle income countries at a disadvantage for vaccine access during an influenza pandemic, which also occurred with COVID-19 vaccines during their initial deployment [45] and during the 2009 H1N1 pandemic [46,47].

The PIP Framework is a mechanism adopted by the 194 Member States of WHO, that aims to ensure, inter alia, equitable access to future pandemic influenza vaccines through 'Standard Material Transfer Agreements 2 (SMTA2s)' which are legally binding contracts between WHO and influenza vaccine manufacturers that receive candidate vaccine viruses developed with PIP biological materials. Through the SMTA2s, WHO secures access to specific percentages of future pandemic influenza vaccine production, in real time, for allocation and distribution to developing countries, based on public health risk and need. As of August 2024, 15 influenza vaccine manufacturers have signed SMTA2s [48], ensuring access by WHO to 11.31 % of the future global pandemic influenza vaccine production (most will be donated to WHO, and some will be provided at an affordable cost to WHO). Such access will promote equity by supporting vaccination of priority groups in countries where there is no local influenza vaccine production and/or supply agreements in place with manufacturers. As with all vaccines donated to, or procured by, UN agencies, the vaccines will need to be prequalified or included in the emergency use listing by WHO. As of October 2024, 11 of the 32 established influenza vaccine manufacturers have at least one influenza vaccine prequalified by WHO. This could facilitate timely prequalification of a future pandemic influenza vaccine from them. There is not currently an emergency use list open for pandemic influenza vaccines.

The development of mRNA and other novel influenza vaccines has potential to support greater pandemic preparedness and vaccine production capacity. mRNA vaccines can be developed quickly, faster than current influenza vaccine platforms, and have been successfully scaled up and distributed in an emergency situation, as demonstrated during the COVID-19 pandemic. Many mRNA influenza vaccine candidates are in development for both seasonal and pandemic influenza (Taaffe et al., unpublished data, 2024) with a few of the seasonal candidates in advanced development; seasonal mRNA influenza vaccines could reach the market in the next few years [7]. Production of seasonal mRNA influenza vaccines would increase global influenza vaccine production capacity, especially when existing mRNA production capacity that was built up for COVID-19 is leveraged, and prior approval of a seasonal mRNA vaccine candidate may facilitate the regulatory process for a pandemic version.

There is a considerable amount of research and development on next-generation influenza vaccines [7]. These include candidates using different platforms (mRNA) and/or different vaccine design approaches to improve the performance of influenza vaccines. In addition to mRNA candidates, other candidates in clinical development have shown promise in improving breadth or duration of protection, easier delivery (oral vaccine [49] and microneedle array patches [50]), and faster production. If successful in their development and approval, there could be increased demand for production of these type of vaccines, including among manufacturers in LMICs, potentially leading to greater vaccination coverage and production capacity. Additionally, more broadly protective vaccines may provide some level of protection to a pandemic virus, offering a stop-gap measure during inter-pandemic periods or at the start of a pandemic, before a closer-matched pandemic vaccine is available. To reflect the evolved R&D landscape and perspectives gained from the COVID-19 pandemic, WHO is updating its Preferred Product Characteristics for Next-Generation Influenza Vaccines. The WHO FVIVA project results, expected in mid-2025, will link up vaccine development, policy decision making and implementation to optimize influenza vaccination programmes worldwide by describing next generation influenza vaccines' potential global public health value and return on investment to manufacturers, funding entities and countries [51].

5. Conclusions

The inevitability of the next influenza pandemic and lessons learned from the COVID-19 pandemic underscores the critical need for robust and equitable vaccine production capacity. While influenza production capacity has overall increased since the inception of GAP in 2006 and this capacity has remained stable since 2019, significant disparities exist. While targeted efforts through GAP to increase production capacity of influenza vaccines in low- and middle- income countries had some success, the bulk of manufacturing capacity is still concentrated in high income countries, which represent 69 % of seasonal capacity and almost 80 % of pandemic capacity. While there is some production in upper-middle income countries (almost 30 % of seasonal capacity and 20 % pandemic) there is still very little production occurring in lower-middle income countries (under 2 % of seasonal capacity and under 1 % of pandemic capacity), and there is a complete lack of capacity in low income countries and in the African region. This imbalance is likely to lead to unequal access to vaccines during a pandemic, exacerbating global health inequities.

Strengthening and expanding current influenza vaccination programmes and encouraging the establishment of programmes where there are none remains a critical activity for maintaining and increasing global influenza vaccine demands and thus production capacity.

Expanding manufacturing technology and building manufacturing capacity in lower-middle income and low income settings are also essential to ensuring that pandemic vaccines can be made and distributed to all populations in need globally. As demonstrated through GAP and other initiatives, building vaccine manufacturing capacity can be a long process, requiring considerable resources and commitment by many actors, and is reliant on a host of factors to be sustainable [52], including consistent local markets. In addition to efforts to diversify production capacity, it is equally important that global, regional, and national procurement and distribution mechanisms be established and strengthened to ensure equitable access to vaccines, especially for those countries that may not have their own production capacity. Moreover, the development and approval of novel influenza vaccines, such as mRNA vaccines, holds promise for increasing production capacity and improving pandemic preparedness. These activities must be prioritized and concerted action between global policy makers, manufacturers, funders and country decision makers needs to be fostered [11] now to secure a future of greater preparedness and equal protection for all against the next influenza pandemic.

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CRediT authorship contribution statement

Jessica Taaffe: Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Shoshanna Goldin:** Writing – review & editing. **Philipp Lambach:** Writing – review & editing. **Erin Sparrow:** Writing – review & editing, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data that has been used is confidential.

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