Global Challenges in Seasonal Influenza Vaccine Supply, Use, and Policy

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Abstract

Seasonal influenza outbreaks occur on every continent, infecting millions and killing around 500,000 patients each year. The 2018 influenza season has been a vicious one—the H3N2 strain is a fast-mutating, aggressive form of the virus, and we have had difficulty immunizing against it. Decreasing the devastation of seasonal influenza starts with smart vaccine systems: a greater supply of doses distributed to the right people. In this review, we evaluate the global threat of seasonal influenza and explore the availability of vaccines as an essential prevention mechanism. We first identify key stakeholders in global influenza policy, vaccine supply, and regional public health governance. Next, we define the extent of the need for vaccines by examining surveillance systems and assessing the current disease burden of seasonal influenza. We examine current challenges in vaccine availability and allocation, and their respective impacts on health outcomes. Finally, we discuss policy implications of supply and allocation studies; we particularly note the promising outlook of communication programs, the advantages of optimized dose distribution, and the need to concentrate on infrastructure in low-income countries.

Introduction

"Vaccines are miracles." Professor Pedro Alonso of the Institute of Global Health, Barcelona explains that just a few dollars spent on immunization can protect an individual from severe disease and disability, making vaccines "one of the best investments in health" (Robert, n.d.). Among the recognized vaccine-preventable diseases (VPDs) is seasonal influenza, an acute viral infection that affects millions of people worldwide every year. Approximately 4 million people will develop severe cases of seasonal influenza this year; about 480,000 will not survive ("WHO | Influenza (Seasonal)," 2018).

Every case is different: some patients present mild symptoms, while other cases require hospitalization or are fatal. The virus is easily spread through infectious droplets in the air, as well as skin-to-skin contact ("WHO | Influenza (Seasonal)," 2018). Its two- to four-day incubation period (before symptoms present) makes transmission highly common, resulting in heightened danger for at-risk groups such as the elderly, young children, and those with underlying medical conditions (Ferguson et al., 2005; "WHO | Influenza (Seasonal)," 2018). Flu season is defined by the annual peak in influenza viral activity; this usually occurs between the months of December and February in the Northern hemisphere and from May to August in the Southern hemisphere, though flu activity may be extremely irregular in tropical climates (CDC, n.d.-b; Cohen et al., 2010; "WHO | Influenza (Seasonal)," 2018). A seasonal epidemic is a rapid spread of illness through nearby communities; epidemics occur annually and are concentrated in particular areas. In contrast, pandemic influenza is defined by its spread across multiple countries or continents, usually affecting a greater proportion of the population; humans typically have little to no immunity to pandemic strains of influenza, since they have not been vaccinated against nor been previously exposed to them (CDC, n.d.-d; Torrey, 2017; "What's The Difference Between An Outbreak And An Epidemic? | IFLScience," n.d.). This review will focus on seasonal flu epidemics, though pandemics likewise deserve significant attention of health policymakers.

Controlling influenza is an issue of utmost public health importance. To combat the devastating impacts of this virus, we must gather an accurate understanding of the global burden of disease; this may be achieved through careful surveillance of virus strain emergence, patient cases, preventive and curative care, and mortality. Of particular importance is the use of vaccines, a prevention mechanism which can drastically reduce influenza incidence, transmission, and deaths. From 2006-2014, immunization for seasonal influenza resulted in over 40,000 deaths averted in the US alone—representing a 22% reduction in the expected mortality (CDC, 2015; Foppa et al., 2015). Unfortunately, access to this life-saving resource is not universal. Especially in low-income nations, vaccine supply remains low, and high-risk groups are being missed by current immunization programs.

In this review, we evaluate the global threat of seasonal influenza and explore the availability of vaccines as an essential prevention mechanism. We first identify key stakeholders in global influenza policy, vaccine supply, and regional public health governance. Next, we define the extent of the need for vaccines by examining surveillance systems and assessing the current disease burden of seasonal influenza. We then examine current challenges in vaccine availability and allocation, and their respective impacts on health outcomes. Finally, we discuss policy implications of supply and allocation studies; we particularly note the promising outlook of communication programs, the advantages of optimized dose distribution, and the need to concentrate on infrastructure in low-income countries.

Key Stakeholders & Major Initiatives

Key players in international health have recognized the urgent need for immunization improvements (see Table 1 for organization acronyms, missions, and main initiatives). The World Health Organization (WHO) has been a long-time advocate for vaccine use; they published the Global Action Plan for Influenza Vaccines (GAP I) in 2006, with a follow-up GAP II in 2011 focusing on technical implementation and strategy refinements (Fig. 1) ("WHO | GAP objectives," 2014; WHO GAP, 2016b). The WHO helped its member nations achieve the goals of GAP I and GAP II by contributing surveillance systems, evaluating current vaccine use and pandemic preparedness, and working with national advisory committees (WHO GAP, 2016b).

Meanwhile, in 2010, the Bill and Melinda Gates Foundation declared a Decade of Vaccines and promised to donate over $10 billion to expand immunization programs to previously missed groups in middle- and low-income countries (Robert, n.d.). In 2012, key stakeholders pledged together and formed the Global Vaccine Action Plan (GVAP), a collaboration between the WHO, UNICEF, the National Institution of Allergy and Infectious Diseases (NIAID), and the Bill and Melinda Gates Foundation.

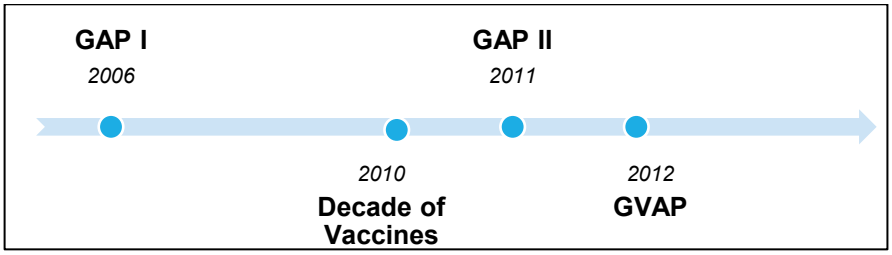

FIGURE 1. Timeline of Major Immunization Initiatives, 2006-present (Robert, n.d.; SAGE, 2017; "WHO | GAP objectives," 2014; WHO GAP, 2016b).

The GVAP connects leaders across the public and private sectors, including multilateral organizations, philanthropic foundations, and policy officials, in order to increase equity in vaccine access and identify gaps in influenza research and policy (Robert, n.d.; SAGE, 2017). By May 2017, 194 countries' Ministers of Health had committed to the GVAP. The major goals of the initiative are to improve immunization program governance, keep better surveillance, and expand vaccination services. Though the yearly WHO progress report of the GVAP does not include seasonal influenza in its detailed supply data for 12 essential vaccines (such as hepatitis B, measles, and rubella), increasing the supply and use of flu vaccines nonetheless remains a recognized item of the action plan (WHO, 2018).

The Strategic Advisory Group of Experts on Immunization (SAGE) evaluated the GVAP in October 2017. They report that "multiple issues at all various levels threaten progress"; some global challenges they identified include the shocks of natural disasters, economic instability, and the migration crisis (The Strategic Advisory Group of Experts (SAGE), 2017; WHO, 2017b). SAGE suggests that the implementation plans must be revised and global participation must be strengthened in order to achieve goals of the GVAP by 2020 (SAGE, 2017).

It seems evident that the attention of international health icons has been captured. Greater challenges arise with the establishment and improvement of immunization programs on the regional and local levels, as international collaborators attempt to see through the lofty goals of the GVAP.

Major Players in the Influenza Vaccine Sphere		
Stakeholders in Policy & Advocacy	**WHO**	World Health Organization. Facilitates global cooperation to combat health crises ("WHO | Alliance vision and mission," 2011). Launched GAP I (2006) and GAP II (2011). Initiated the GVAP in 2012.
	UNICEF	United Nations International Children's Fund. Works to improve the well-being of every child (UNICEF, n.d.). Signed onto the GVAP, 2012.
	CDC	Centers for Disease Control and Prevention. Promotes disease prevention strategies, evaluates health systems, and conducts public health research in the United States (Rouse, n.d.). Signed onto the GVAP, 2012.

	NIAID	National Institute of Allergy and Infectious Diseases. Works to "understand, treat, and prevent infectious, immunologic, and allergic diseases" ("NIH: National Institute of Allergy and Infectious Diseases | Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases," n.d.). Signed onto the GVAP, 2012.
	The Bill and Melinda Gates Foundation	Foundation with a mission to work towards health equity in order to respect the value of each human life ("Who We Are - Bill & Melinda Gates Foundation," n.d.). Launched the Decade of Vaccines in 2010; joined the GVAP in 2012.
	SAGE	Strategic Advisory Group of Experts on Immunization. Oversees and evaluates WHO work involving immunization. Established in 1999 (WHO, 2017b).
	GISRS	Global Influenza Surveillance and Response System. Responsible for monitoring global influenza activity, forecasting pandemics, and identifying strains for the annual flu vaccine ("WHO | Global Influenza Surveillance and Response System (GISRS)," 2018).
Global Initiatives	**GAP I**	Global Action Plan for Influenza Vaccines (I). Three objectives were to increase seasonal vaccine use, increase production capacity, and expand research and development ("WHO | GAP objectives," 2014; WHO GAP, 2016b).
	GAP II	Global Action Plan for Influenza Vaccines (II). 2011 follow-up of GAP I, focusing on pandemic preparedness and technical implementation ("WHO | GAP objectives," 2014).
	Decade of Vaccines	2010-2020. Initiative of The Bill and Melinda Gates Foundation to

		expand vaccine research and programs. Set precedence for GVAP (Robert, n.d.).
	GVAP	Global Vaccine Action Plan. International, multilateral initiative to improve immunization programs and surveillance (SAGE, 2017).
Vaccine Supply	**GAVI**	Global Alliance for Vaccines and Immunization. Maintains stockpile of vaccines for 47 developing countries. Plans to immunize 300 million children by 2020. Permanent membership board includes UNICEF, WHO, The Bill and Melinda Gates Foundation, and The World Bank Group (GAVI, n.d.-a, n.d.-b, n.d.-c).
	Sanofi Pasteur, Novartis, Seqirus, ID Biomedical, GlaxoSmithKline	Major producers of influenza vaccines. Supply mostly to North American and European regions (Australia Fluvax GSK Belgium FluarixNH Fluarix Butantan & Mutagrip Vaxigrip Tetagrip Sanofi Pasteur, 2009; WHO, 2003).

TABLE 1. Key players in influenza vaccine supply, policy, and initiatives (Australia Fluvax GSK Belgium FluarixNH Fluarix Butantan & Mutagrip Vaxigrip Tetagrip Sanofi Pasteur, 2009; GAVI, n.d.-a, n.d.-b, n.d.-c; "NIH: National Institute of Allergy and Infectious Diseases | Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases," n.d.; "WHO | Alliance vision and mission," 2011; "WHO | GAP objectives," 2014; "WHO | Global Influenza Surveillance and Response System (GISRS)," 2018; "Who We Are - Bill & Melinda Gates Foundation," n.d.; Robert, n.d.; Rouse, n.d.; SAGE, 2017; UNICEF, n.d.; WHO, 2003, 2017b; WHO GAP, 2016b).

Assessing the Disease Burden of Seasonal Influenza

Global Influenza Surveillance and Response System (GISRS) and Collaborators

Surveillance of seasonal influenza is critical to driving policy decisions about vaccine composition, supply, distribution, and administration. It is crucial that surveillance be kept up-to-date and specific on the national, regional, and global levels. The current leading surveillance system is the WHO Global Influenza Surveillance and Response System (GISRS), which monitors influenza activity and uses its inter-pandemic data to forecast potential threats ("WHO | GAP objectives," 2014). National Influenza Centers from 101 GISRS-participating countries provide live

surveillance of influenza by collecting abundant samples, analyzing their compositions, classifying them by sub-type, and disseminating their findings through the FluNet web system ("WHO | FluNet - CHARTS," 2016).

These efforts are complemented by a handful of major WHO collaborating centers and laboratories, which have more specialized roles such as managing regulations and studying the ecology of influenza in animals ("WHO | GAP objectives," 2014). CDC programs also provide significant assistance to nations in strengthening their surveillance systems and expanding their capacities for sample testing. The CDC partnered with 39 nations between 2004 and 2009, and facilitated substantial improvement in influenza diagnostics and sentinel surveillance (i.e., sampling influenza-like illnesses to test for the presence of influenza) (Polansky, Outin-Blenman, & Moen, 2016).

The GISRS is also responsible for determining which strains of influenza will be selected for the seasonal vaccine each year. They use the aggregate data from FluNet and collaborators to recognize trends in the global circulation of influenza, perform antigenic analyses using isolates, and determine where further local research is needed ("WHO | GAP objectives," 2014). Creating flu vaccines is an inexact science; it relies heavily on predictive analysis, and there is no guarantee that the chosen strains will be the same strains present in the population when flu season comes along[1]. In fact, there is a 4- to 6-month delay from the time a strain is selected to the time vaccines are generally available—plenty of time for mutation of the strains in vaccine production and changes in viral activity among the population. Keeping consistent, extensive databases is essential to ensuring the most accurate estimates of flu activity and vaccine strain selection, though there always remains a degree of uncertainty as to how seasonal influenza will affect the population during a given year.

Current Global Disease Burden

FluNet most recently published data from the January 8-21, 2018 collection period and found that 60% of the strains were categorized as influenza A. Overall, according to the recent report, there is relatively high influenza activity in the northern hemisphere temperate regions, while the

[1] *Why are some annual influenza vaccines less effective?* We start the vaccine-making process by picking a strain of the virus which we believe will be of high risk during flu season; the vaccinated population will be theoretically protected against this disease. To make the vaccine, various strains of the influenza virus are injected into chicken eggs, where the virus replicates for several days (CDC, n.d.-c; Medlock & Galvani, 2009). Fluid is then extracted and put through a number of purification processes (CDC, n.d.-c). There is a 4- to 6-month delay from the beginning of this process to the time vaccines are widely available (CDC, 2015; Foppa et al., 2015; WHO, 2017a). The virus mutates at a fast rate while growing in the chicken eggs; additionally, a different strain could become a greater threat in the meantime (Medlock & Galvani, 2009). Essentially, the strain we originally intended to protect against, the strain the vaccine covers, and the strains present in the environment during the time of flu season (several months later) may all be different from each other—thus, our vaccines may not effectively protect the population.

southern hemisphere temperate zone levels remain at typical inter-seasonal levels ("WHO | Influenza update - 308," 2018). However, recent Australian reports note record-high levels of influenza activity—of particular concern, the number of confirmed influenza cases (as of October 2017) is four times greater than it was during 2009 H1N1 pandemic—suggesting that the northern hemisphere may face a catastrophic influenza season in the coming months (Paules, Sullivan, Subbarao, & Fauci, 2018). Only time will tell whether the 2018 influenza season will be one of historic severity.

As referenced earlier, the WHO publishes estimates for the annual global influenza burden: **the 2017 epidemic resulted in about 3 to 5 million severe cases, along with 290,000 to 650,000 deaths** ("WHO | Influenza (Seasonal)," 2018). However, we must also consider secondary complications of infection; thousands more deaths may be attributable to conditions that arise from or are worsened by influenza infections, namely streptococcus pneumoniae and non-respiratory conditions such as cardiovascular disease or diabetes (Cohen et al., 2010; Madhi, Klugman, & Vaccine Trialist Group, 2004; Frellick, 2017). We must not neglect these indirect outcomes when assessing the burden of influenza epidemics, though cause attribution of these cases is difficult to monitor (Cohen et al., 2010).

Why Vaccines?

The main goal of vaccination is to prevent transmission, and therefore the minimize the disease burden across populations. Vaccination not only protects the vaccine recipients from acquiring the illness, but also offers an indirect benefit to the nearby unvaccinated population: it decreases the potential number of infected individuals they may come in contact with (Medlock & Galvani, 2009). If a large proportion of the population receives vaccines, we may achieve herd immunity: where disease outbreak is minimized through vaccinating most, but not all, of a population (Kim, 2014; NOVA, n.d.). Immunized individuals are uninfected and incapable of transmitting the disease to others, thereby protecting the greater "herd".

However, in order for the impact of herd immunity to be fully realized, we must vaccinate a sufficient proportion of the population. Contagious, widespread diseases like seasonal influenza can circulate rapidly and infect millions due to our highly mobile modern society. For these reasons, we must assess current coverage rates, supply availability, and distribution trends so that we might identify weaknesses in our systems and become better equipped to immunize the global population.

Vaccine Supply

Immunizing the global population for seasonal influenza requires extensive infrastructure for vaccine manufacturing. Though complete recent data on global vaccine supply is not always available, we may use previous studies and mathematical models to estimate current stocks and

production capacity. Following this, we must also consider what may prevent vaccines from reaching the target populations.

Population Coverage for Seasonal Influenza Vaccines

The International Federation of Pharmaceutical Manufacturers and Associations Influenza Vaccine Supply (IFPMA IVS) task force conducted a study of global vaccine supply, from 2004-2009. They analyzed data from 157 countries, evaluated their epidemic preparedness based on WHO guidelines, and identified key determinants of influenza vaccine supply levels. A United Nations population group used previous WHO recommendations to calculate a 15.9% "hurdle" rate, above which a nation would be considered to have an adequate supply of vaccines. The IFPMA IVS study found that only 20% (31 of the 157 countries) had adequate vaccine supplies according to this recommendation. The study further revealed that two-thirds of the participating countries did not have enough vaccines to cover 10% of their national populations. Worse yet, more than one-third of the 157 did not distribute enough vaccines to cover even just 1% of their populations (Palache, 2011). These staggeringly low coverage rates are especially alarming in the face of annual influenza epidemics which show no signs of subsidence.

Global Trends in Dose Distribution

Global supply studies indicate major disparities in vaccine distribution. Just 5% or less of seasonal influenza vaccines are distributed to 50% of the world's population, residing in mostly low- and middle-income countries in Africa, Southeast Asia, and the Eastern Mediterranean Region (Fig. 2) (Duque, McMorrow, & Cohen, 2014; Palache et al., 2017).

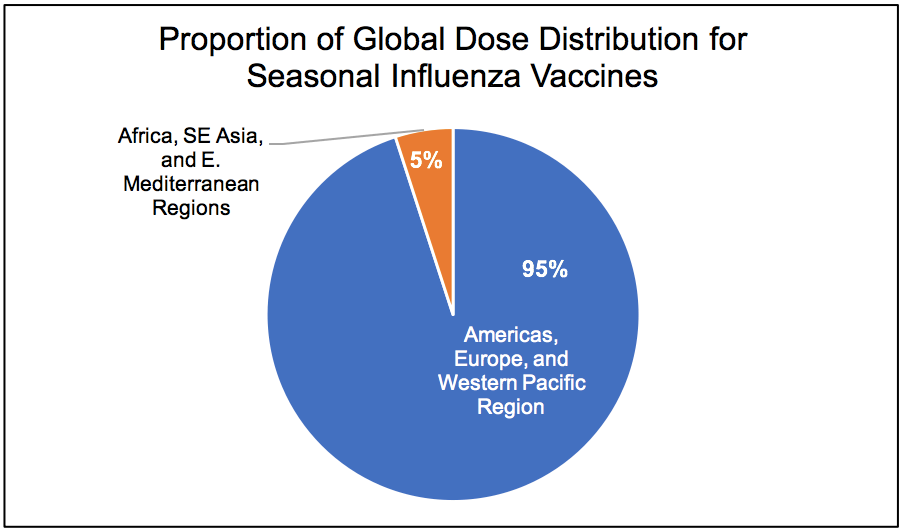

FIGURE 2. Global Dose Distribution for Seasonal Influenza Vaccines, 2017 (Duque et al., 2014; A. Palache et al., 2017).

Let us focus on that small slice of the figure, representing half of the world's population. In many parts of Africa, limited immunization governance and product supply hinder vaccination rates. A study evaluating existing African public health programs reported that just 45% of surveyed countries had any seasonal influenza vaccines available, only 30% of these countries had guidelines or policies for their use, and the sole four countries with coverage data only had enough vaccines to cover 0.5-2% of their populations (Duque et al., 2014).

For perspective, we might look at U.S. vaccine coverage: across all age groups, approximately 145 million individuals were vaccinated for the 2016-2017 influenza season, representing about 45% of the national population (CDC, n.d.-a). Beyond those who were vaccinated, there was an excess of vaccine supply. Needless to say, seasonal influenza vaccines are widely available—and widely promoted—in most parts of the United States, and immunization rates remain relatively high. It is imperative that we focus global attention on countries with next-to-nothing coverage rates, in order to begin the long process of closing the gap in influenza vaccine access.

Vaccine Production Monopolies

The IFPMA IVS study offered useful observations of varying vaccine supply allocation across the globe and provided insight as to how particular regions succeeded in meeting adequate dose distribution. First, they noted that 75-80% of vaccine supply is concentrated in the Americas[2] and Europe. Additionally, these regions accounted for 72% of global influenza vaccine supply growth during the study period (2004-9). This abundance of supply can be largely explained by the disproportionate presence of manufacturers, compared to other regions. Another study reports that in the 2009-10 flu season, 80% of vaccines came from 7 major manufacturers in industrialized nations[3] (Partridge & Kieny, 2010a). As of 2010, there were *zero* vaccine producers in the Eastern Mediterranean Region, nor on *the entire continent of Africa*. Production monopolies give industrialized regions, particularly North America and Europe, an immense advantage when it comes to immunizing their populations

[2] In the U.S., 6 major types of seasonal vaccines—both trivalent and quadrivalent (covering 3 and 4 strains of the virus, respectively)—are offered by 4 main manufacturers: Seqirus, Sanofi Pasteur, ID Biomedical Corp. of Quebec, and GlaxoSmithKline ("Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2017-18 Summary of Recommendations GROUPS RECOMMENDED FOR VACCINATION," 2017).

[3] Partridge and Kieny reports, "For the 2009–2010 Northern hemisphere epidemic, seasonal trivalent vaccine was produced predominantly in three of the six WHO regions. Of the 573 million doses of trivalent vaccine produced, 49% (283 million doses), 26% (151 million doses), and 23% (133 million doses) were produced in EUR, AMR, and WPR [West Pacific Region], respectively" (Partridge & Kieny, 2010).

(Partridge & Kieny, 2010). As one would expect, access to vaccines is aided by presence of major manufacturers (i.e., increased supply).

Growing Production Capacity, Underutilized Resources

Though only mentioned briefly in the IFMPA IVS study's conclusion, one crucial thought to keep in mind is that production capacity for influenza vaccines is much higher than current production levels. From 2009-2011, there was a 65% increase in influenza vaccine production capacity, yet only an 8% increase in actual production (Partridge & Kieny, 2013).

Vaccine production capacity has seen significant growth over the past two decades (Fig. 3). In 2006, Emanuel & Wertheimer estimated an annual global influenza vaccine production capacity of 425 million (Emanuel & Wertheimer, 2006), while dose distribution was about 360 million (Palache et al., 2017). Vaccine distribution peaked in 2012 at 620 million doses, but has decreased slightly since then (Palache et al., 2017; WHO GAP, 2016a). As of 2015, global production capacity stood at an all-time high of 1.47 billion doses and continues to grow (Palache et al., 2017; WHO GAP, 2016a). Today, we see a recurrent trend of increasing production capacity, though actual production of vaccines lags behind.

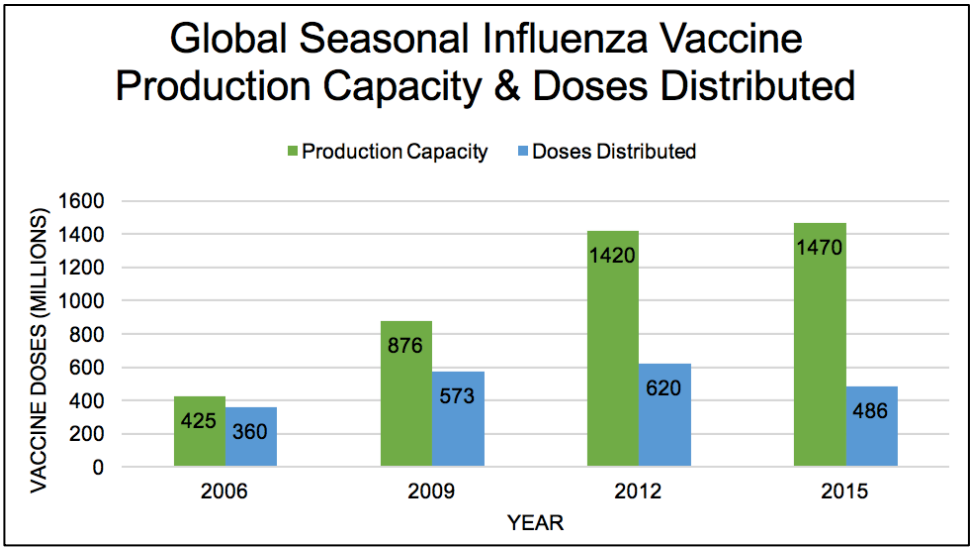

FIGURE 3. Global Seasonal Influenza Vaccine Production Capacity vs. Doses Distributed, 2006-2015 (Emanuel & Wertheimer, 2006; McLean, Goldin, Nannei, Sparrow, & Torelli, 2016; Palache et al., 2017; Partridge & Kieny, 2010, 2013; WHO GAP, 2016b).

It is important to note that these results indicate dose distribution to hospitals and clinics, not the actual use of the vaccines. Dose distribution data still provide useful estimates for determining approximate immunization rates of the various populations under study (Palache, 2011).

Barriers to Vaccine Uptake

A vaccine's journey from the production facility to the recipient's body is long and complex, with many opportunities for error. Figure 4 illustrates a potential set of challenges (among many others) which may hinder vaccine uptake.

Production of multivalent vaccines (i.e., with multiple components/strains), like those for seasonal influenza, is a complicated process which requires extensive technical machinery and expensive manufacturing costs. Making the initial batch, filling numerous types of syringes, packaging each product, and labeling them in multiple languages is only the beginning of the endeavor; companies must also worry about licensing their products in various countries and markets, establishing cold-chain delivery systems[4], and facilitating global distribution (Office, 2007; Smith, Lipsitch, & Almond, 2011). In order to avoid producing an excess of vaccines (and suffering major financial losses), some manufacturers produce well below their capacities, aiming to meet "just below" demand. Especially when a flu epidemic worsens in the latter months of the winter season, the delayed demand is not met with adequate supply—this may have dangerous consequences. The manufacturers have the freedom to produce as many or as few vaccines as they wish, according to their business interests; luckily, bulk purchase assurances from organizations like UNICEF help to stabilize the annual demand and prevent major shortages of vaccine supply (Office, 2007; Smith et al., 2011).

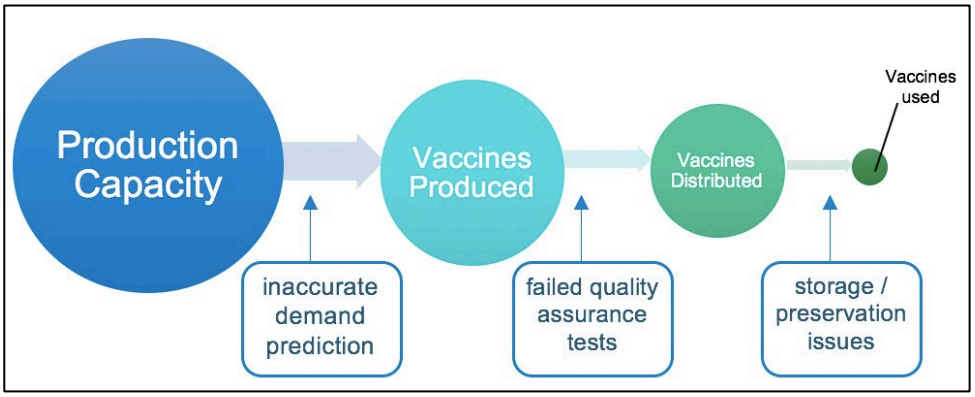

FIGURE 4. Vaccine production lags behind manufacturing capacity; this limits the stock that may be distributed globally and eventually administered to individual patients (Palache, 2011).

**Note: The relationship between production capacity and vaccines distributed is depicted to scale; "vaccines produced" and "vaccines used" shape sizes are approximations* (Palache et al., 2017; WHO GAP, 2016a).

[4] Influenza vaccines must be stored between 2-8 degrees Celsius and remain refrigerated from their initial production to their eventual usage. This is called the "cold-chain" preservation system.

Beyond the production stage, there exist several other reasons why a vaccine might not be eventually administered: there might be delays from medical supply distributors, insufficient delivery personnel, defective refrigeration equipment, limited access to the health clinics, or simply a lack of cultural awareness or support of yearly influenza vaccines (Office, 2007; Smith et al., 2011).

These trends in seasonal influenza vaccine production are similar to those of basic infant vaccines, like polio and measles. According to Smith et al., for diseases like these, "global manufacturing capacity is adequate" and incomplete coverage "primarily results from the need for better delivery infrastructure" (Smith et al., 2011). We must work to improve our delivery systems at all levels, from the factories to the patients, in order to capitalize on these life-saving products.

Case Study: Seasonal Influenza in the Elderly, U.S. and South Africa

There exist major disparities in global immunization coverage and resulting health outcomes. Examining influenza in elderly populations of the United States and South Africa provides us with a pertinent example of this inequity.

The U.S. has one of the highest rates of elderly influenza vaccination; currently, 70% of the 65+ population has been vaccinated in the past year (Center for Health Statistics, n.d.). Just a few years back, in 2010, when 65% of the U.S. senior population received flu vaccines, only 15% of their counterparts in South Africa had been immunized (Cohen et al., 2010; van Vuuren, Rheeder, & Hak, 2009). The elderly are at high risk due to their compromised ability to fight infection and their susceptibility to further respiratory complications; consequently, influenza mortality rates are highest among the 75+ population (Iuliano et al., 2017). An elderly person in South Africa is four times more likely to die of influenza than an elderly person in the U.S.; over all ages, influenza-related deaths are three times more likely to occur in South Africa (Cohen et al., 2010). Vaccine availability is of urgent concern for high-risk groups like the senior population, and few countries attain comparable vaccination rates as the U.S. for these groups.

Policy Implications: Communication Programs

Per Capita Income NOT Directly Correlated with Vaccine Availability

Though production monopolies may lead to greater vaccine access, studies have shown that manufacturing capacity is not the sole determinant of vaccine availability—and neither is World Bank income status. A study of 31 African countries found that World Bank income level was *not*, in fact, correlated with vaccine availability (Duque et al., 2014). Similarly, the IFPMA IVS study of 157 countries found that dose distribution was *not* directly correlated with per capita income of the countries under study. Of particular note, several Latin American countries, namely Mexico and Chile, are "less developed," yet they still reached the aforementioned

"hurdle" rate (enough vaccines to cover 15.9% of the total population). How did they do it?

Communication & Education Programs: A Promising Solution?

The IFPMA IVS study examined factors that may correlate with adequate vaccine supply, in a sub-analysis of countries with established vaccine policies. They found that countries with wide-scale communication activities were most likely to have reached the hurdle rate for influenza vaccine supply (5.3x more likely than countries without such programs). The next highest-ranking correlated variable of vaccine provision was reimbursement, meaning there was funding available for vaccines and/or administrative costs associated with their distribution. Both of these correlations were significantly stronger than that of development status (Palache, 2011).

Compared with having official policy recommendations alone, countries with programs directly influencing patients are about four times more effective at vaccine provision (Palache, 2011). These programs may include public communication about vaccine administration, education about viruses, campaigns emphasizing the benefits of herd immunity (i.e., how high vaccination rates can protect a whole population), as well as options for funding.

In conclusion, adequate supply of influenza vaccines may be aided by production monopolies, but it is not associated with higher per capita income. What does this mean? Fortunately, these findings provide reassurance that achieving higher immunization rates does not necessarily require major economic change within a country. Instead, we can use policy measures, such as public education and communication programs, to increase demand and provision of vaccines.

Optimizing Allocation

In any case, where there is a limited supply of vaccines, we must focus on allocating these products effectively. The question that then arises is: what is considered to be an "effective" distribution of vaccines? Should we prioritize the elderly, to minimize the total number of flu-caused deaths? Or, focus on children, since they would lose more potential years of life if they did not survive?

Medlock and Galvani describe vaccine distribution as "a complex issue lying at the intersection of public health, economics, and ethics" (Medlock & Galvani, 2009). They created a model to determine the optimal distribution of vaccines, based on five outcome measures: deaths, infections, years of life lost, "contingent valuation"[5], and economic costs[6]. Using data and inferences from the 1918 and 1957 influenza pandemics,

[5] Contingent valuation: a value system in which young adults are most valued, based on their utility in society (Medlock & Galvani, 2009)

[6] Economic costs included the costs of vaccination, treatment, as well as the lost economic value of those who die of influenza (Medlock & Galvani, 2009)

they sought to determine how many vaccines would be required to protect the U.S. population against a severe epidemic.

They determined an optimal distribution, incorporating a combination of these outcome measures while also considering transmission dynamics. According to their optimized model, only 62-63 million vaccines would be required to evade an influenza epidemic, compared to the 85 million vaccines distributed in the US at this time. Since transmission rates are highest among school-aged children, vaccines should be provisioned to this age group, along with adults ages 30-39 (their parents), who often act as transmission "middle men" between the infected youths and the adult population (Medlock & Galvani, 2009).

They supported this conclusion by analyzing the CDC recommendations for flu vaccine provision. The expansion of prioritization from children 0-5 (pre-2008) to children 0-18 (post-2008) was projected to result in an estimated 19% reduction in infections and a 9% reduction in mortality. However, there are two conditions under which age-based allocation of vaccines should instead shift to focus on the elderly: when vaccine supply is low (since vaccinating the elderly, who have the highest mortality risk, would minimize the death rate), and when the vaccines are not very effective (therefore, protecting against transmission among kids would be a less effective approach)[7] (Medlock & Galvani, 2009).

All in all, rethinking the way vaccines are distributed across national populations will help us minimize both disease burden and unnecessary economic waste.

Critical Groups

To tackle the broad challenge of low immunization rates, we cannot simply use a one-size-fits all approach. Certain regions of the world and demographic groups require more attention currently; the populations in danger will change over time, as will their levels of need. Two of these critical groups include populations in lower income countries, namely in Africa, as well as children under the age of five.

Africa & Low-Income Countries

Though studies have found that vaccine availability is not correlated with per-capita income, influenza-related mortality nonetheless has a disproportionate effect in low to middle-income countries. A WHO representative explains that limited healthcare and surveillance infrastructure in developing nations means we often do not have accurate data on mortality, though a recent modeling study using available surveillance data and death records suggests that influenza-related mortality is highest in sub-Saharan Africa (2.8 to 16.5 per 100,000 people) and Southeast Asia (3.5 to 9.2 per 100,000) (Iuliano, Roguski, Chang, et al., 2017; Frellick, 2017). This disparity in regional mortality was

[7] see footnote 1 (page 7) for information on vaccine effectiveness

especially evident in the 1918 and 1957 pandemics, as well as the H1N1 swine flu pandemic of 2009, during which 51% of deaths occurred in Africa and Southeast Asia (Dawood et al., 2012; Duque et al., 2014). Limited access to health care, prevalence of underlying conditions, and crowded living conditions likely contributed greatly to this increased mortality (Cohen et al., 2010; WHO, 2003).

A recent survey of African public health experts indicated that disease burden and availability of international funding were the strongest motivators of policy. While outside organizations and political officials often turn to displayed efficacy of vaccines and cost-benefit analyses to motivate policymakers, these arguments are seen as less compelling to the African health experts (Duque et al., 2014). As Cohen et. al describes, "The perception that influenza does not cause substantial mortality in Africa may contribute to the underutilization of influenza vaccines, antivirals, and other control measures in this setting" (Cohen et al., 2010).

We must focus our efforts towards strengthening surveillance systems in low and middle-income countries, which will allow health officials to better understand the disease burden in their countries and capture policymakers' attention. Likewise, awareness of a large disease burden may further motivate international agencies to contribute funding for vaccines and antivirals. In addition, improved surveillance infrastructure will allow for more accurate estimates of global mortality rates and improve epidemiologists' ability to predict "hot spots" for new strains of the virus, among other valuable contributions.

Children Under Five

The youngest members of our global population are at great risk for influenza infection. There are about 90 million new cases of seasonal influenza each year in children under five, plus an additional 20 million cases of flu-associated acute lower respiratory infection (ALRI). Mortality estimates are rather vague, though a 2008 study suggests that 28,000-111,500 children under five die of flu-related causes each year, and 99% of these deaths occur in developing countries (Nair et al., 2011).

Unfortunately, these high mortality rates do not come as a big surprise, as vaccination rates remain low. 20% of children born each year are missed by immunization programs; this means that 1 in 5 kids do not receive basic protection against life-threatening illnesses like whooping cough, hepatitis B, polio, and others. 70% of these children reside in 10 countries, most of which are in Africa (Cashin-Garbutt & Elder, n.d.). A global effort to provide basic vaccines for these lethal illnesses will have multi-fold effects. First, of course, we protect the health of our children from the given diseases and make small steps towards health care equity. Beyond this, once we build and develop vaccine supply and distribution programs in resource-poor regions, this infrastructure can then be used to implement seasonal influenza vaccine programs.

Conclusions & Looking Ahead

Major Implications

Increasing seasonal influenza vaccine use has broader implications beyond reducing the annual winter disease burden. We must keep in mind that pandemic viruses may arise from mutated seasonal viruses at any given moment, and global mortality risk could skyrocket in a matter of weeks to months (WHO, 2017b). It is crucial that seasonal vaccine production continues and expands so that manufacturers are prepared to meet elevated demand in future pandemics (Palache, 2011; WHO, 2003). To prepare for such pandemics, the WHO established the Pandemic Influenza Preparedness (PIP) Framework in 2011, recently reviewed in 2016. Member nations and companies share viral strains that are suspected to lead to a pandemic, pay an annual sum to the WHO, and agree to give a portion of their vaccine/antiviral supply to the WHO. The aggregate contribution of pandemic influenza vaccines/antivirals constitutes 10% of the global supply, which the WHO distributes directly to low-income countries ("Review of the Pandemic Influenza Preparedness Framework Report by the Director-General," 2017; WHO, 2017a). Through these efforts, the PIP Framework collaborators actively work towards equity in vaccine distribution.

Summary of Findings

Seasonal influenza is a dangerous acute viral infection with a significant global disease burden. The WHO estimates that 3-5 million people were severely infected and 290,000-650,000 people died during the 2017 seasonal epidemic ("WHO | Influenza (Seasonal)," 2018). Key stakeholders in vaccine policy and initiatives include the WHO, CDC, and the Bill and Melinda Gates Foundation; together with other collaborators, they launched the Global Vaccine Action Plan, in order to increase immunization rates for various diseases worldwide. The Global Influenza Surveillance and Response System (GISRS) uses extensive data from numerous contributors to assess the global disease burden and identify the viral strains to be included in each yearly flu vaccine.

Vaccines are essential to preventing disease transmission and controlling the morbidity of seasonal influenza. However, only 20% of countries have adequate vaccine supplies to immunize enough of their populations (15.9% coverage) to manage seasonal epidemics (Palache, 2011). Vaccine manufacturers are concentrated in the Americas and Europe; these two regions receive about 80% of global seasonal influenza vaccine supply, while hundreds of low- and middle-income nations are left behind. However, two studies found that having adequate vaccine coverage did not, in fact, directly correlate per capita income, and that dose distribution may be improved through public campaigns and education programs (Duque et al., 2014; Palache, 2011). This is good news on the policy front—we can use these communication programs to

improve vaccination rates instead of relying solely on major development status advances.

In the meantime, using modeling studies allows us to more efficiently distribute vaccines across populations by prioritizing high-risk individuals and active transmitters, such as school-aged children, adults 30-39, and the elderly (Medlock & Galvani, 2009). Additionally, we must concentrate our attention towards equity in vaccine distribution, particularly focusing on those in low-income nations as well as all children under the age of five.

Vaccinating the global population against influenza and other illnesses will involve a combination of "political commitment, scientific innovation, significant funding, close international cooperation, and partnerships among WHO, member states, donor institutions, vaccine manufacturers, and other stakeholders" (Partridge & Kieny, 2010). Active global collaboration is critical to improving influenza-related health outcomes; we must urgently address the major immunization inequities before the disease burden becomes too great to bear.

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