Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Major Article

The long road of pandemic vaccine development to rollout: A systematic review on the lessons learnt from the 2009 H1N1 influenza pandemic

Alex Asamoah Ankomah MBChB, MIDI/MPH [a,*], Aye Moa PhD [b], Abrar Ahmad Chughtai MBBS, PhD [a]

[a] School of Population Health, University of New South Wales, Sydney, New South Wales, Australia
[b] Biosecurity Program, Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia

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Background: The 2009 Influenza A(H1N1) pandemic prompted one of the largest public health responses in history. The continuous emergence of new and deadly pathogens has highlighted the need to reflect upon past experiences to improve pandemic preparedness. The aim of this study was to examine the development and rollout of 2009 influenza A(H1N1) pandemic vaccine and knowledge challenges for the effective implementation of vaccination programs for COVID-19 and future influenza pandemics.

Methods: A systematic review was conducted searching EMBASE (inception to current date) and PUBMED (from January 2009 to current date) databases for relevant published studies about influenza A(H1N1) pandemic vaccines. A Google search was conducted to identify relevant documents from gray literature. Selected Studies were reviewed and summarized.

Results: A total of 22, comprising of 12 original studies and 10 relevant documents met the inclusion criteria. Fourteen papers reported an initial high demand that outweighed production capacity and caused vaccine shortages. Vaccine procurement and supply were skewed toward high-income countries. Low vaccination rates of about 5%-50% were reported in all studies mainly due to a low-risk perception of getting infected, safety concerns, and the fear of adverse effects.

Conclusions: Safety concerns about the approved H1N1 vaccines resulted in many unsuccessful vaccination campaigns worldwide. Understanding the factors that influence people's decision to accept or refuse vaccination, effective risk communication strategies, adequate resources for vaccine deployment initiatives and building local capacities through shared knowledge and technology transfer may help to improve COVID-19 vaccine uptake and accelerate pandemic control.

BACKGROUND

Traditionally, vaccine development is an extensive, long, and expensive process with no assurance of success despite the significant financial and human resources utilized.[1] In past, vaccine development for epidemics - severe acute respiratory syndrome coronavirus (SARS-CoV), Ebola virus and Zika virus were only completed during the post-pandemic phase thereby causing huge financial loss to manufacturers, wastage of allocated funds by countries, and a significant setback of other relevant vaccine development programs.[2]

With COVID-19, the urgency emanating from the increasing trends in morbidity and mortality has led to significant changes in already established timelines among vaccine developers so as to provide successful candidates to the world as quickly as possible. At least 7 vaccines across 3 distinct platforms have currently received approval for emergency use and rolled out in many countries.[3] The World Health organization (WHO) reports an additional 200 candidates in development with about 76 in different clinical phases of development globally over the past year.[4] Most countries are initially targeting vulnerable groups for vaccination.[5] However, there still exists many unresolved concerns with these approved vaccines such as the possible appearance of variant strains resistant to the current

* Address correspondence to Alex Asamoah Ankomah, MBChB, MIDI/MPH, School of Population Health, University of New South Wales, Sydney, NSW 2052, Australia.
E-mail address: ankomahalexankomah@gmail.com (A.A. Ankomah).

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vaccines. Additionally, technical challenges in building the capacity for the production of billion doses of vaccines, and ethical concerns associated with the provision of vaccines to poor countries remain an imminent challenge.[3]

Although there have been multiple previous influenza pandemics, experts were faced with similar new experiences in 2009 as a result of the emergence of a novel H1N1 virus.[6] New COVID-19 vaccines have been developed and rolled-out in a relatively short period of time. Despite many controversial discussions and public concerns on these approved vaccines, it is observed that most of the global focus is on developing and/or improving newer, experimental approaches to aid in vaccine development within the shortest possible time. There is limited attention among the scientific community, manufacturers and other stakeholders on the lessons that can be learnt from past epidemics and/or pandemics to inform current and future vaccine research, development and rollout.[7]

This review aimed to examine vaccine development and rollout during the 2009 Influenza A (H1N1) pandemic to gain a better understanding of the experiences encountered and to highlight specific lessons learned from this past pandemic to support current COVID-19 vaccination programs as well as future pandemics.

METHODS

Search strategy

A systematic review was conducted adhering to the guidelines on Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[8]

Two main search strategies were employed. First, the systematic search to identify relevant peer-reviewed articles was conducted using: EMBASE (since inception to current date) and PUBMED (from January 2009 to current date). Primary studies providing original quantitative and/or qualitative data on the 2009 Influenza A H1N1 pandemic vaccine development and rollout were sought during the search. Although the WHO from October 2011 recommends the use of influenza A(H1N1)pdm09 as a standardized nomenclature, a broad search strategy was adopted to identify all relevant articles in which 2009 H1N1 pandemic vaccines were described and relevant to the areas of discussion in this review since other names were used prior to WHO recommendation.[9]

The EMBASSE search terms used included: subject headings "2009 H1N1 influenza" OR "2009 adj4 (H1N1 or influenza or flu or pandemic)" OR "2009 adj4 (swine flu or swine influenza or swine-origin)" AND "vaccin* adj4 (implementation or uptake or rollout or roll-out)." The PUBMED search included the terms "2009 influenza pandemic (H1N1 subtype), vaccine development" to identify all relevant papers. A manual search of the reference lists of selected studies was also undertaken to recognize other relevant papers. The search was however limited to only human studies.

As a second search strategy, a Google search was done to identify other relevant documents from gray literature including reports from health departments, and other relevant health organizations. The search terms: "2009 pandemic influenza (H1N1 subtype), vaccine development," "2009 pandemic influenza (H1N1 subtype), vaccine development WHO," 2009 pandemic influenza (H1N1 subtype), vaccine development CDC' and 2009 pandemic influenza (H1N1 subtype), vaccine development ECDC' were used in the general search, and limited to the first 6 pages obtained for each of the 4 search terms used in Google.

Eligibility (inclusion and exclusion) criteria

Inclusion criteria

- Primary studies or gray literature that reported on the 2009 Influenza A(H1N1) pandemic vaccines according to the 3 main areas of discussion: (1) the vaccine research and development process, (2) the availability and accessibility of vaccines in relation to pandemic timelines and (3) implementation, rollout and uptake of H1N1 vaccines in 2009, including the limitations and challenges. Original papers evaluating pandemic immunization activities in 2009/2010 in the post-pandemic period were included.
- Only papers published in English language within the stipulated time-period and were accessible online.
- Population: General population of any country and studies that also focused on at-risk and target populations such as health care workers, children, and adolescents. pregnant women and people with underlying chronic conditions.
- Studies on multiple influenza strains that reported specific (non −aggregate) data on H1N1 pandemic vaccines or vaccination.

Exclusion criteria

- Studies describing intentions or willingness to receive H1N1 vaccines or institutional capability and willingness to produce H1N1 vaccines prior to, during or after the pandemic phase with no data on the actual R&D process or pandemic vaccination activities.
- Secondary data sources.
- Immunogenicity, safety or clinical efficacy of H1N1 vaccines.
- Unrepresentative and/or small study samples such as case series and/or reports, editorials, letters, and opinion papers.

Data extraction and assessment

The identified articles and gray literature were exported into Endnote X9. Both reviewers independently screened articles by titles and abstracts to identify relevant papers for full review. Potentially relevant articles were read by both reviewers independently to determine the final selection of relevant articles for inclusion. For gray literature, all first 6 pages in Google were similarly screened in 3 stages: title, abstract (when available), and full-text screening against the eligibility criteria. The detailed selection process used in the study is outlined in the PRISMA flow diagram in Figure 1. Data extracted for each article included the author and/or study year, study design or any theoretical model employed, study size, data collection methods including time periods, study participants, and the study outcomes. The data extracted from relevant gray literature included the author and/or study year, institution involved, aims and objectives of the report and the outcomes reported. The eligibility criteria and template for extraction were adhered to strictly by both reviewers to ensure consistency. All findings including discrepancies were discussed among all reviewers to arrive at the final selection.

RESULTS

A total of 1,056 papers were identified from all sources. From database searches, 816 articles were identified of which 41 articles were selected for full review after removal of duplicates and review of titles and abstracts. From the 240 papers identified from Google

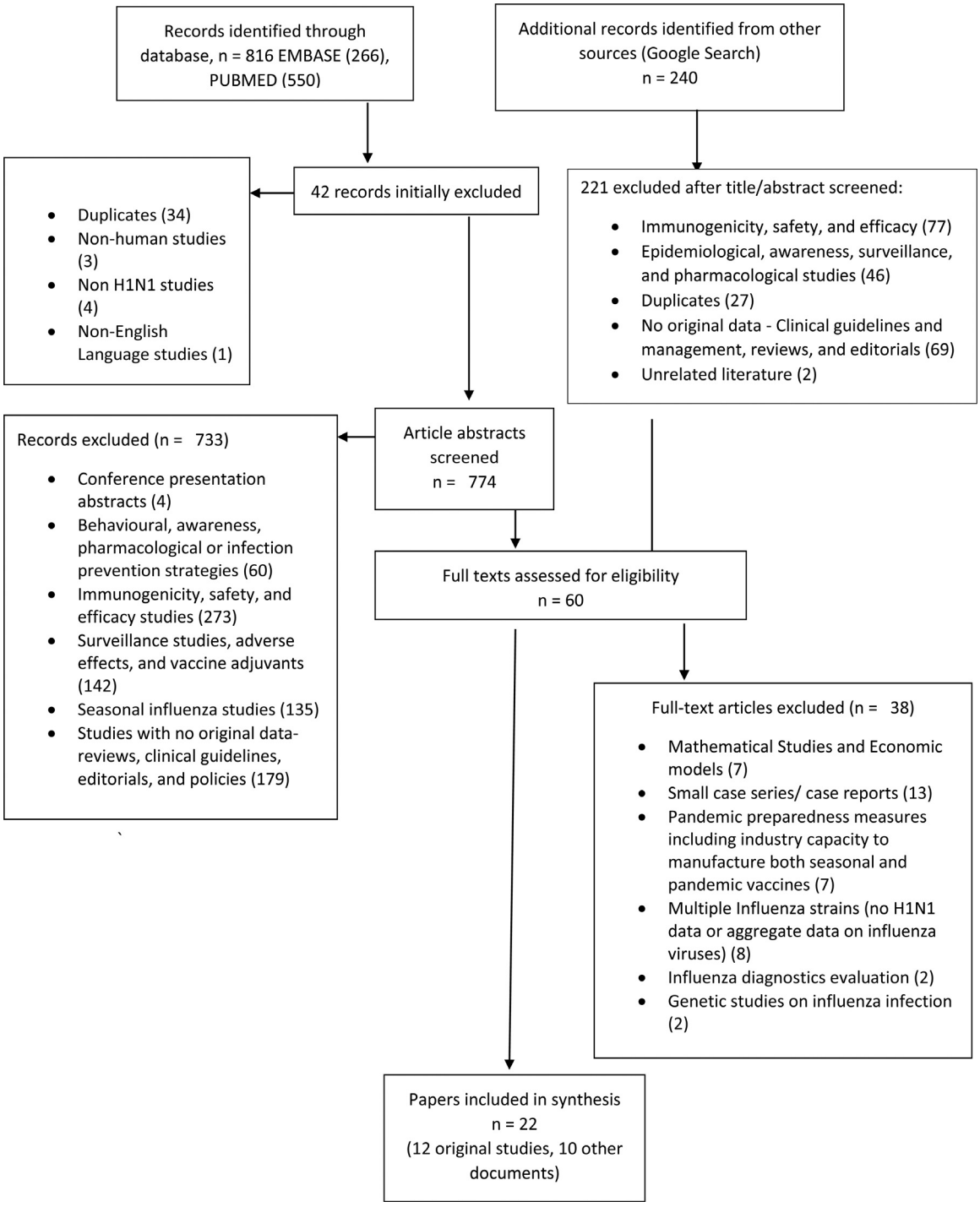

Fig 1. PRISMA flow diagram for the search strategy and selection process.

and screened, 19 of gray literature were selected for full text review. Finally, a total of 22, which included 12 primary studies and 10 of gray literature that met the eligibility criteria were included in the review. A summary of the selected papers is presented separately for original studies and gray literature in Table 1 and 2, respectively.

Reporting of vaccine availability in relation to the pandemic timelines and specific immunization programs launched in various countries varied across papers. Different methodologies and at-risk or target population studies were observed. For articles, individual study findings were provided and, in some cases, relevant national estimates and targets also reported. The 2009 global vaccine R&D events were also presented with significant highlights on the activities undertaken by the WHO, CDC, and ECDC in the initial stages of the pandemic.

Fifteen papers reported on the availability and access to safe vaccines during the pandemic with 6 describing diverse

Table 1
Summary of original articles included in the review

Author and/or y of study	Study type and/or methodology	Study participants	Main findings	Comments
Chor et al., 2011	Cross-sectional study	2,100 health care workers (HCWs) from Hong Kong (HK), Singapore (SG), and United Kingdom (UK). Response rate of 27.1% (HK), 94.5% (UK), and 94.7% (SG).	Low vaccine uptake in all 3 countries (from 13%-41%). A strong predictor of vaccine acceptance being a previous personal history of seasonal vaccination: HK OR: 9.215 (6.232-13.625, $P < .001$), SG OR: 9.221 (4.35-19.546. $P < .001$), UK OR: 17.698 (5.778-54.207, $P < .001$).	Low response rate from Hong Kong (27.1%).
Alsaleem, 2012	Cross-sectional study	402 primary health care workers in the Kingdom of Saudi Arabia. Response rate of 86.3%.	Low vaccination uptake (28.2%) due to vaccine safety concerns and fear of side effects. Knowledge of H1N1 Influenza and awareness of vaccines was generally low among participants, however, better in physicians than other HCWS.	Good response rate and the use of a validated questionnaire in the study.
Giannattasio et al., 2015	2- Phase cross-sectional face-to-face survey. Response rate of 73%.	400 HCWs in a tertiary care university hospital in Southern Italy for phase 1. 352 participants used in Phase 2 due to retirement of older staff.	Low vaccination rates. Safety concerns and efficacy of influenza vaccines reported as the main reasons of vaccine hesitancy.	Provides a comparative analysis of 4 different influenza seasons among a heterogenous health care population.
Head et al., 2012	Survey	221 HCWs in the UK Response rate of 7.2%.	59% vaccination rate with many HCWs refusing vaccines due to concerns with clinical effectiveness, and fear of side effects. Personal risks assessments critical to vaccine acceptance and uptake among HCWs.	Low participation rate. May not be representative of all HCWs however, useful data on vaccination programs among HCWs in the UK.
Hothersall et al., 2012	Cross-sectional study	205 front-line HCWs working in Shropshire County's general practice services. 48% response rate.	Vaccination uptake among participants for pandemic influenza (83.9%) was significantly higher than national uptake (40.3%), regional (40.9%), and counties (49.3%).	Low response rate. Sampling bias and response bias may threaten the validity of the study.
Barrière, 2010	Cross-sectional study	506 HCWs and non−HCWs. 26.2% response rate.	Overall vaccination rate was 51.4%. Age, prior seasonal influenza vaccination, professional category, and source of information identified as strong predictive factors for pandemic influenza vaccination.	Low participation rates, selection bias may be present due to high vaccination rates among study participants.
Klaiman, 2014	Qualitative study: in-depth interviews	20 Local Health Departments identified as high achievers from the school-based vaccination clinics.	Successes can be attributed to an established, constant, and trusting relationship between the health departments, school districts, and parents of school children.	13 out of 20 results from school-based vaccination clinics are analyzed.
Kumar, 2012	Online self-administered survey	2,079 American adults (18 y and over) randomly selected from the US Knowledge Networks (KN) online research panel. Response rate of 56%.	Overall vaccination rate of 8.4% (95% CI: 15.6-21.5). Variables at all levels of the Social Ecological Model influenced vaccine uptake with the strongest being at the interpersonal, intrapersonal, and institutional levels.	Using a theoretical framework in a novel way to comprehensively study vaccine uptake among adult populations.
Lohiniva, 2014	Qualitative study: in-depth interviews (open-ended questions) and focus group discussions	123 pregnant women in their second or third trimesters	Vaccination rates remained low among pregnant women (41%) caused by widespread rumors, misconceptions, and conspiracy theories in Morocco. Underlying these issues were the cultural and religious influences of the community.	Although limited study sample size, incorporating both rural, and urban perspectives gave diverse views.
Freund et al., 2011	Prospective cohort study	A randomly selected sample of 882 pregnant women between 12- and 35 wk gestational age.	Majority of French pregnant women did not vaccinate (62.9%) and were found to be mostly immigrants and those with low socioeconomic status. Non−vaccination was associated with geographic origin, profession, smoking behaviors, and previous history of seasonal influenza vaccination with immunization rates consistent with national estimates (77%)	A quantitative assessment of a failed vaccination program in Paris.
Tarrant, 2013	Multi-center cross-sectional study design.	Five hundred forty-nine new mothers admitted to the postnatal units of 4 geographically and socio-economically distributed public hospitals	Extremely low vaccination rate of 6.2% among pregnant women due to fear of side effects and safety concerns. Sources of information during the pandemic integral to vaccine uptake.	Response rate not provided.
Schwarzinger et al., 2010	Cross-sectional study	2,253 French adult population aged 18-64 y, randomly selected from an online research of French households managed by IPSOS Interactive Services.	The general perception of low risk counteracted the messages by public health authorities on the need to vaccinate.	Risk perception directly influences vaccination uptake.

components of the R&D phase of 2009 H1N1 pandemic vaccines. Seventeen reported on vaccine implementation programs launched in respective countries including Saudi Arabia, Hong Kong, Italy, United Kingdom, Australia, France, Morocco, and United States of America.

Vaccine research and development

Three papers reported that active manufacturing processes to produce the monovalent H1N1 influenza pandemic vaccines were conducted by the same influenza vaccine companies that produce seasonal influenza vaccines in the USA, Australia, China, Russia, India, and the European Union.[1,10,11] Also, 1 reports that new manufacturers contributed to vaccine development in some Asian countries including Japan and Korea Republic.[10] Three papers indicated that alongside the traditional approach of production with chicken eggs, a new culture biotechnology was used in the manufacture of cell-derived pandemic vaccines which were also distributed to many countries during the pandemic.[1,11,12] Five papers mentioned the development and approval of 4 vaccines in the US and European Union countries.[1,11-14] However, the CDC also reported a fifth pandemic vaccine that was also approved by the Food and Drugs Administration (FDA) in the US 2 months after approval of the initial 4 vaccines.[13] In the United Kingdom, 2 pandemic vaccines namely Pandemrix (GlaxoSmithKline) and Celvapan (Baxter) were initially approved for use in a 1 dose and 2 dose-schedule, respectively.[14] As of February 2010, 30 different vaccines from eleven vaccine developers had received licenses for public use globally.[1]

Availability and accessibility of vaccines in relation to pandemic timelines

Three reported that averagely, vaccines were introduced 3-6 months after WHO declaration of the pandemic in June 2009.[1,10,11] The approved vaccines became available in September 2009 in both Australia and the US,[1,13,15] November 2009 within European Union countries,[1,10-12] and December 2009 in Hong Kong [16] after the rate of infections, hospital admission and deaths had reduced substantially due to the non−pharmaceutical interventions instituted in these countries. Five papers reported substantial delays in accessing approved vaccines due to initial limitations in the vaccine supply chain worldwide. [11,12,15,17,18] Access to approved vaccines was discussed in eleven papers and this varied significantly among countries all over the world in relation to timeliness and quantity of vaccines.[1,10-13,15-19] The variation was largely influenced by 3 main factors: the existence of advanced purchasing agreements between manufacturers and individual countries, availability of financial resources to support direct vaccine procurement and delivery and the involvement of negotiating international agencies and vaccine donors. The introduction of a WHO deployment initiative to support low-resourced countries resulted in 122.5 million vaccine doses pledged by wealthier nations and vaccine manufacturers however, a total number of 78 million doses donated to developing countries as of November 2010.[19]

Implementation, roll-out, and uptake of pandemic Influenza A(H1N1) vaccines

According to twelve papers, implementation of vaccination varied greatly among nations and were implemented mainly by General Practitioners, Primary health care providers, public health authorities, and other services like the Red Cross.[10,15-17,20,21] The roll-out of vaccines during the 2009 pandemic was characterized by an initial increase in the demand for vaccines by nations but declined as the pandemic progressed.[13] Three papers reported that most countries opted for a single dose for adults instead of the 2-dose schedule in order to vaccinate more people and procured multi-dose vials to prevent further delays.[13,15,17] Five reported that national vaccination coverages were low and ranged averagely from 5% in WHO-assisted countries to about 50% in the UK and Sweden.[1,11,14,19,22] Four papers reported low vaccination coverage among pregnant women and health care workers who were high-risk groups and targeted for vaccination. Vaccine coverage for pregnant women was 6.2% in Hong Kong[16] and median coverage of 21% in WHO-assisted African countries[18] whiles that of heathcare workers was 28.2% in Saudi Arabia,[23] 17% in Italy,[24] and median covergae of 9% in WHO-assisted African countries.[18] Nine reported that globally, the refusal of vaccines was mainly due to the fear of side effects, poor or no counselling from health care providers and a common perception that vaccines were unnecessary due to the mild clinical nature of the infection.[14,16,22-25] In Morocco, belief in pandemic conspiracies were also rife.[26] In the UK and Singapore where uptake was relatively higher (35%-45%), vaccine acceptability was influenced by physician recommendation, higher educational and socioeconomic status, family and social support, personal protection, history of past seasonal influenza and fear of transmission to patients, friends, and family.[25,27]

DISCUSSION

This review has found that the emergence of the novel H1N1 virus in 2009 prompted one of the largest public health responses in history resulting in a relatively shorter timeframe of vaccine development and the successful implementation of vaccination programs globally. Most of the successful responses mounted were guided by the scientific knowledge acquired from influenza research and development conducted for many years prior to 2009 and country-specific pandemic preparedness plans that were in place for future influenza pandemics. However, there was generally a low uptake of the available vaccines due to safety concerns, widespread doubts on the clinical efficacy of approved vaccines, and a general perception of a low health risk due to the moderate severity of H1N1 influenza in 2009. The lower the perception was of being at risk of contracting influenza, the lesser the likelihood was of getting vaccinated against pandemic influenza. The evidence showed that vaccine uptake was strongly influenced by multiple factors including risk perception, access to vaccination centers, past vaccination history, demographic factors such as occupation, education, socioeconomic status and sociocultural beliefs and values of the community. Therefore, there is a need to critically consider, and understand these factors that influence an individual's decision to either accept or refuse vaccination in order to mount a successful vaccination program.

A lesson learnt is that although purchasing agreements reduce the complex and time-consuming negotiations that will otherwise occur during emergency situations, these direct agreements that may occur before or at the initial stages of a pandemic contribute significantly to the persistent inequitable vaccine distribution between rich and poor countries during pandemics. In 2009, challenges with vaccine supply were widespread and mostly affecting countries with very limited access to the approved vaccines.[28] Most of the manufacturing capacity had been procured by wealthier nations through direct pre-existing agreements with manufacturers such that, vaccines were scarce for countries that had no contracts with developers.[29] More than a decade after, equitable vaccine access and supply remains a major topic of discussion even in the current COVID-19 pandemic suggesting that this lesson from 2009 may have been ignored. Current data shows that wealthier countries representing only 14% of the world population have already secured 53% of the leading COVID-19 vaccine candidates both approved and in clinical trials such that they are able to vaccinate their total population by 3-5 times over by 2021.[30] As such, we are currently experiencing an unequal supply and rollout

Table 2
Summary of relevant documents of gray literature included in the review

Author and/or y of publication	Institution(s) involved	Aims and objectives and/or target	Findings	Comments
Abelin, 2011	The International Federation of Pharmaceutical Manufacturers and Associations International Vaccine Supply taskforce (IFPMA IVS); European Manufacturers group (EVM)	Evaluation of the role of vaccine manufacturers during the 2009 influenza pandemic response elucidating the lessons learnt from the 2009 vaccine industry experience.	Global reliance on previous extensive work on influenza vaccines for the successful development of at least 30 H1N1 vaccines in a timely manner.	An industry perspective from active industry players during the 2009 pandemic.
CDC, 2010	Centers for Disease Control and Prevention (CDC)	Providing highlights of the CDC-related events and response during the pandemic	Recommendations on clinical management guidelines, antiviral therapy, vaccine development, risk assessment, and risk communication were core activities undertaken by the CDC.	A chronological summary on the CDC pandemic response in 2009 in the US.
Fizzell, 2010	Pandemic (H1N1) Influenza Vaccine Team, New South Wales Department of Health, Australia.	Detailed description provided on NSW pre-pandemic planning and implemented vaccination program including successes and challenges encountered.	The intended mass vaccination centers were substituted for General Practice and Aboriginal Health Service-based model for vaccine delivery due to the mild nature of the pandemic and the availability of vaccines after the peak of infections.	Gives a good account of the NSW state's activities during the 2009 pandemic. No reports on other Australian state activities
Girard et al., 2010	World Health Organization	Evaluating the production, scale-up, safety, immunogenicity, and efficacy of H1N1 pandemic vaccines in 2009/2010 including novel technologies developed for manufacturing.	Global manufacturing processes initiated in May 2009 including new Asian developers in April 2009. Vaccines produced were safe, well-tolerated with few reported adverse effects.	Aspects of immunogenicity, safety and efficacy of vaccines not in scope of this study
Hanquet et al., 2010	Belgian Medicine Agency and the Belgian Inter-Ministers Influenza Cell. Participating institutions include EMA representatives, WHO, the European Commission (DG Sanco), the European Centre for Disease Prevention and Control (ECDC) and 7 European countries	Exploring the European experiences and lessons from the 2009 pandemic vaccine development activities to inform future pandemic preparedness.	Country-specific variations made to the pandemic response to meet individual country needs in 2009. Effective communication and collaborations are needed as part of pandemic preparedness.	Provides the experiences and impacts of vaccination in different European countries.
Mei et al., 2013	Shandong University: Department of Health Care Management and Maternal and Child Health	A review and summary of past influenza outbreaks vaccine development including H1N1 and policies to serve as reference guide for future pandemic activities.	Marked improvements observed with policies to manage influenza outbreaks, drug stockpiling, and vaccine development. Faster and well-coordinated responses by industry players are essential to the prevention and control of emerging infectious diseases.	Adequate data provided on H1N1 vaccines in report
Mihigo et al., 2012	WHO Collaborating with the Regional Office for Africa -Republic of Congo	Summary of H1N1 vaccine delivery and immunization programs in Africa during the 2009 pandemic. Reported adverse effects also discussed.	WHO delivered 32.18 million doses of A (H1N1) pdm09 vaccine in Africa in 2010 although there were delays in distribution. Delays in finalizing donation agreements, logistical issues, negotiating contracts -waiving manufacturer liability, and instituting proper deployment plans to avoid wastage as reasons for delays.	Only 14 countries provided data on vaccine implementation and use in respective countries.
Ropero-Álvarez et al., 2012	Pan American Health Organization (PAHO)	Describing pandemic influenza (H1N1) vaccine preparation, procurement and use in Latin American countries (LAC).	Pandemic preparedness plans in LACs were in place but with minimal focus on vaccines. High vaccination coverage achieved but with significant variations within individual countries in the region.	Region with one of the largest vaccine implementation programs instituted in 2009/2010
WHO, 2012	World Health Organization	A chronological account of WHO activities that ensued prior to and during the 2009 influenza pandemic.	The WHO Deployment Initiative became the first global, multi-sectoral, coordinated response enhancing access of the pandemic vaccines to low-resource countries. A total of 122.5 million doses of vaccines were to be procured through donations and negotiations on behalf of eligible low-income countries.	Report on only WHO donor vaccines to poor countries. Specific country initiatives for receiving donated vaccines are not discussed.
Johansen et al., 2009	European Union	A review of the composition of approved vaccines in the EU.	Generally, vaccines were safe, effective, and well- tolerated with post-marketing surveillance mechanisms instituted for possible adverse effects following immunization (AEFI).	Report limited to only the initial 4 vaccines developed in the EU.

of COVID-19 vaccines worldwide with recent shortages in many low-resourced countries that continue to face high COVID-19 morbidity and mortality. Pre-pandemic purchasing agreements were not in place (or possible) for COVID-19 as this was a completely novel virus, however, many direct agreements have already been made such that low-income countries are unable to secure additional vaccines in a timely manner despite international support from vaccine deployment initiatives. Rather than the usual reactive deployment initiatives like WHO deployment initiative in 2009 and COVID-19 Vaccine Global Access (COVAX) in 2020, the formal establishment of an international institution on behalf of developing nations fully equipped with resources including adequate funds from international donors (as part of pandemic preparedness) and nations during emergencies to mediate direct agreements with manufacturers is urgently needed as this will provide surety to vaccine manufacturers of potential buyers at the end of vaccine development and manufacturing efforts and aid in preventing massive shortages in regions that are most challenged during pandemics. It is important to acknowledge that challenges with vaccine supply particularly in low-resourced settings are bound to occur due to the increased global demand. In 2009, the inequitable vaccine distribution and access that occurred during the pandemic was later mitigated when a single-dose vaccine became available which allowed many more people to receive protection against H1N1 virus from a single shot.[29] Single-dose vaccines may not always be feasible, but this is currently available for the COVID-19 pandemic with the Johnson & Johnson vaccine which offers a unique opportunity for public health authorities to get more people fully vaccinated against COVID-19 infection especially those in areas with shortages whilst minimizing challenges with having to secure 2 vaccine doses per person. Additionally, this single-shot vaccine is stable, and can be kept at refrigerator temperature thereby minimizing challenges with cold storage in these low-resource settings.[5] Collaborated efforts are further needed to streamline the long bureaucratic processes associated with vaccine donations to poorer countries to improve timeliness and promote equitable access to pandemic vaccines in current and future pandemics. Furthermore, the recognition of regulatory and approval mechanisms between countries will minimize the barriers associated with licensing, and supply of approved vaccines.

We also learn that emerging technologies arising from long-standing influenza vaccine R&D have offered the scientific and pharmaceutical community an opportunity to increase preparedness against the constant threat of pandemic influenza. Thus, highlighting the importance of continuous investments in vaccine R&D as part of pandemic preparedness. In 2009, a new cell culture-derived biotechnology was used in developing H1N1 vaccines which were licensed for use globally. Many experts opine that this new approach used in 2009 coupled with other on-going research for live recombinant and subunit pandemic influenza vaccines have greatly improved industry knowledge on influenza vaccine immunology and aided in speeding up vaccine development processes when new influenza strains emerge.[31] Similarly, messenger (mRNA) vaccine technology has been researched extensively for many decades in many viruses to improve industry expertise in this area.[5] The onset of the COVID-19 pandemic rapidly escalated R&D investments in this area thereby, aiding mRNA vaccines to be successfully developed for coronaviruses. mRNA have now been approved for human use in the current COVID-19 pandemic.[32] Global prioritization of vaccine development and immunization as integral components of the pandemic preparedness is essential for individual and community protection against the continuous threat of dangerous pathogens. More financial investments are required to support vaccine development for other emerging and re-emerging infectious diseases with no commercially available vaccines. Moreover, efforts should be aimed at sharing the knowledge, technology transfer, and building capacities within low-resourced countries to enable vaccine development for global use.

In 2009, many target groups refused H1N1 vaccines due to concerns on the safety of approved vaccines, media conspiracy, misinformation, and the risk of adverse effects. The lesson learnt is that during planning, a careful consideration of the underlying factors that influence vaccine acceptance or hesitancy, effective risk communication, and education strategies have the advantage of building public confidence in vaccination. So far and on a good note, there has been a high COVID-19 vaccine uptake in many countries like the UK, Canada and Israel.[33] However, vaccine hesitancy still remains a major concern. Reasons for vaccine refusal given in 2009 have been identified as threat to current COVID-19 vaccination targets with many, including health professionals sharing safety concerns and also questioning the speed of development of the vaccines.[34] Therefore, urgent collaborations with relevant stakeholders such as the media and health care professionals should be undertaken to improve knowledge among these stakeholders on the available vaccines and help in the dissemination of right information to the public. Additionally, vaccine implementation activities should be adapted to suit the sociocultural, economic, and political contexts of a country to achieve pandemic control.

This is the first review to our knowledge that comprehensively examines available literature on the 2009 Influenza A(H1N1) pandemic from vaccine development to the rollout and uptake of vaccines. It highlighted important aspects that may have been ignored but useful to improve the current COVID-19 response and offers guidance as part of pandemic preparedness for future responses. Several limitations are present in this study. Comparing these 2 viruses might be flawed in that, the processes for developing these vaccines differed greatly as influenza vaccine development has longstanding production methods that can easily be utilized for new influenza pandemic strains, vs a completely novel coronavirus. The evidence presented does not cover all countries that manufactured H1N1 vaccines and implemented vaccination campaigns. Although these limitations are present, the 2009 findings were consistent from different regions and countries included in the study and as such, the lessons learnt from the past pandemic are valuable for informing the current COVID-19 pandemic and future pandemics.

There was limited data obtained from lower- and middle-income countries (LMIC) on the 2009 H1N1 pandemic vaccine rollout and uptake which would have provided extra valuable information on experiences faced in poor countries during pandemics. This paucity of evidence available from LMIC emphasizes the need for further research to strengthen the current evidence available.

CONCLUSION

The rapid development of vaccines during the 2009 H1N1 pandemic using both existing egg-based and novel cell culture-derived technology demonstrates the significant advancements in vaccine research and development. However, the inequitable distribution of vaccines coupled with inadequate manufacturing capacity to meet global demands led to an initial scarcity of approved vaccines in many poor countries and subsequently, a low uptake of approved vaccines due to safety concerns and fear of adverse effects. More than a decade after, similar events of inequitable distribution and scarcity of vaccines in developing countries are being experienced in the current COVID-19 pandemic and continues to threaten a high uptake of COVID-19 vaccines. Therefore, global and regional collaborative efforts aimed at knowledge and technology transfer, prioritizing COVAX support and stronger policies are urgently needed to increase production capacity and support the equitable distribution of

vaccines which is essential for pandemic control in the shortest possible time.

ETHICAL APPROVAL AND/OR CONSENT TO PARTICIPATE AND/OR CONSENT FOR PUBLICATION

Not applicable.

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