Use of an inactivated vaccine in mitigating pandemic influenza A(H1N1) spread: a modelling study to assess the impact of vaccination timing and prioritisation strategies

V Sypsa[1], I Pavlopoulou[2], A Hatzakis (ahatzak@med.uoa.gr)[1]
1. Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, Athens, Greece
2. Paediatric Research Laboratory, Faculty of Nursing, Athens University, Athens, Greece

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The impact of prioritisation and of timing of vaccination strategies on reducing transmission of pandemic influenza A(H1N1) was evaluated in a community with the structure of the Greek population using a stochastic simulation model. Prioritisation scenarios were based on the recommendations of the United States Centers' for Disease Control and Prevention Advisory Committee on Immunization Practices and vaccination was assumed to initiate either before or during the ongoing epidemic. In the absence of intervention, an illness attack rate (AR) of 34.5% is anticipated. Vaccinating the priority groups before the epidemic (pregnant women, people who live with or care for children <6 months of age, healthcare/emergency services personnel, children 6 months–4 years old and high-risk children 5-18 years old) will have a negligible impact on the overall AR. Vaccinating the recommended groups before the epidemic (priority groups as well as all persons 6 months–24 years old and high-risk individuals 25-64 years old) is anticipated to result in overall and age-specific ARs within the range of seasonal influenza (5%-15%). Initiating vaccination early during the epidemic (AR≤1% of the population) is predicted to result in overall ARs up to 15.2%-19.9% depending on daily vaccination coverage rates. When vaccination is initiated at a later stage (AR: 5%), only coverage of 80% of the whole population at intensive daily vaccination rates would be able to reduce ARs to approximately 15%.

Introduction

On 11 June 2009, the World Health Organization (WHO) raised the pandemic alert level to phase 6 and declared A(H1N1) influenza the first global pandemic of the 21st century. Delays in the development, production and licensure of a vaccine for the current pandemic as well as restrictions in the global manufacturing capacity dictate careful planning of strategies concerning prioritisation and distribution policies. Another important issue to be considered is the timing of vaccination during an ongoing pandemic. Previous modelling studies investigating the impact of various strategies for mitigating a potential pandemic have shown that the benefit of vaccination depends closely on the time it is initiated [1,2].

In the current study we employ a simulation model to investigate the impact of vaccination strategies and of vaccination timing on the overall illness attack rate (AR) of pandemic influenza A(H1N1) in a small community.

Methods

The simulation model

We have used a discrete-time stochastic individual-based simulation model employed previously to simulate A(H1N1) spread [3]. Model parameters were chosen such as to yield age-specific attack rates, in the absence of intervention, similar to that observed in the A(H1N1) outbreak in the community of La Gloria in Mexico [3]. A structured model community of approximately 2,000 people was generated to match the age-distribution, household size and number and size of schools of the Greek population. The model community of 2,000 people was divided into four neighbourhoods of approximately equal size that share one kindergarten, one primary school and one high school. Influenza was introduced at day 0 by randomly assigning a number of initial infective individuals, and person-to-person transmission probabilities were used to simulate influenza spread over time. As the population was assumed to be structured (households, schools, neighbourhoods and community), different transmission probabilities applied to different mixing groups. They were highest for contacts within households and lower for contacts within schools, followed by neighbourhoods and, finally, the entire community [3]. In the absence of intervention, a proportion of symptomatic individuals (80%, 75% and 50% of preschool children, school-age children and adults, respectively) were assumed to stay at home and withdraw from the remaining mixing groups (schools, neighbourhoods, community).

Vaccine efficacy

We have modelled key vaccine efficacy parameters defined previously, i.e efficacy for infection-confirmed symptomatic illness (VE_{SP}), efficacy for susceptibility (VE_S) and, given infection, efficacy for illness (VE_P) and efficacy for infectiousness (VE_I) [4]. Based on estimates from previous trials on the efficacy of homologous inactivated vaccines [5-14], we have assumed a VE_{SP} of 80% for individuals 2-64 years old and of 60% for children 6-24 months and adults >= 65 years old. Estimates for VE_S and VE_P

for individuals 2-64 years old were obtained from Basta *et al.* [15] (40% and 67%, respectively) with a modification in the case of children 0-24 months old and elderly to yield a lower VE_{SP} (VE_S=20% and VE_P=50%).

Vaccination strategies

Four vaccination scenarios, based on the United States Centers' for Disease Control and Prevention Advisory Committee on Immunization Practices (CDC's ACIP) recommendations [16], were evaluated (Table 1). In all scenarios, 80% vaccination coverage was assumed (total coverage). High-risk groups included individuals with chronic respiratory diseases (including asthma), chronic cardiovascular diseases, chronic metabolic disorders (including diabetes mellitus), chronic renal and hepatic diseases and immunosuppression.

Timing of vaccination

All scenarios were evaluated under the assumption that vaccination takes place early enough so that the vaccinated persons have developed immunity before the introduction of pandemic influenza A(H1N1) in the community. Selected scenarios were further explored assuming that 2%, 6% and 10% of the 2,000-persons community are vaccinated daily (daily coverage) and the first vaccinated individuals develop an immune response when the AR reaches 1%, 5%, 10% or 15% of the population.

Results

Effectiveness of vaccination strategies

In the absence of intervention, an AR of 34.5% is anticipated [3]. Vaccinating the priority groups would reduce the AR to 28.0% (Table 2). Under the scenario of vaccinating the recommended groups, the estimated AR is anticipated to be reduced below 10% (AR: 9.6%). When vaccination is extended to all individuals aged between 25 and 64 years, the AR is estimated to be reduced to 2.7%. Offering vaccination additionally to individuals >= 65 years of age is not anticipated to further lower the AR (AR: 2.5%).

The age-specific attack rates under these vaccination strategies are depicted in the Figure. Vaccinating the recommended groups results in low attack rates in all age groups (9.4%, 10.2%, and 8.1% for 0-24, 25-64 and 65+ years, respectively). When vaccination is extended to include also all individuals aged between 25 and 64 years, low attack rates are predicted for all age groups (5.0%, 1.5% and 2.7% for 0-24, 25-64 and 65+ years, respectively). Offering

Table 1

Evaluated vaccination strategies proposed by the Centers' for Disease Control and Prevention Advisory Committee on Immunization Practices [16] in a community of 2,000 people representative of the Greek population

1. Priority groups		2. Recommended groups		3. Recommended groups + 25-64 years		4. Whole population	
Target groups	% of the whole population	Target groups	% of the whole population	Target groups	% of the whole population	Target groups	% of the whole population
Pregnant women	1.0%	Pregnant women	1.0%	Pregnant women	1.0%	Pregnant women	1.0%
Household contacts of children younger than 6 months of age	1.7%	Household contacts of children younger than 6 months of age	1.7%	Household contacts of children younger than 6 months of age	1.7%	Household contacts of children younger than 6 months of age	1.7%
Health care and emergency services personnel	0.9%	Health care and emergency services personnel	0.9%	Health care and emergency services personnel	0.9%	Health care and emergency services personnel	0.9%
Children 6 months-4 years	4.3%	Persons 6 months-24 years	28.9%	Persons 6 months-24 years	28.9%	Persons 6 months-24 years	28.9%
High-risk children 5-18 years	0.9%	High-risk individuals 25-64 years	4.9%	Individuals 25-64 years	53.8%	Individuals ≥25 years	70.5%
Total*	**6.6%**	**Total***	**28.5%**	**Total***	**66.7%**	**Total***	**80.3%**

*Estimated in 200 simulations assuming vaccination coverage of 80% within each target group

Table 2

Simulated illness attack rates and effectiveness of different vaccination strategies based on the Centers' for Disease Control and Prevention Advisory Committee on Immunization Practices [16] in a community of 2,000 people representative of the Greek population

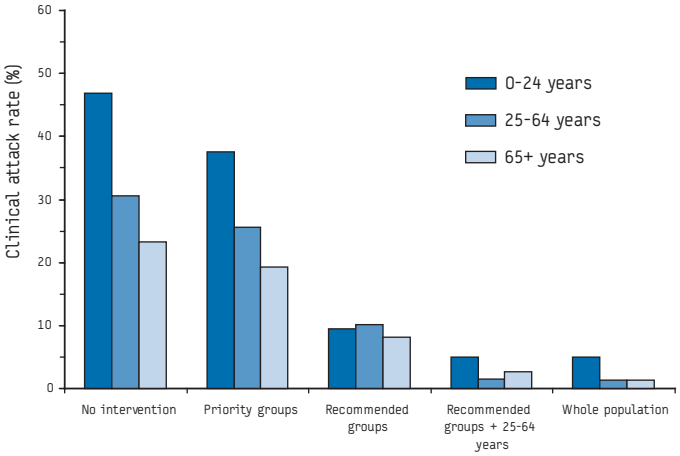
Target population	Attack rate (AR)	(% decrease)*	Number of vaccinations /1,000 persons	Number of cases prevented/person vaccinated
Priority groups	28.0%	(18.8%)	66	0.96
Recommended groups	9.6%	(72.2%)	285	0.86
Recommended groups + 25-64 years old	2.7%	(92.2%)	667	0.47
Whole population	2.5%	(92.8%)	803	0.40

Note: The model assumes 80% vaccination coverage of the target populations and that vaccinated persons become immune before the start of the epidemic
*Compared to an AR of 34.5% in the absence of intervention

vaccination to individuals ≥65 years of age is not anticipated to offer a notable additional benefit for this age group (Figure).

Figure

Age-specific clinical attack rates according to the implemented vaccination strategy, pandemic influenza A(H1N1) 2009



Note: The model assumes 80% coverage of the target groups and that vaccination takes place early enough so that the vaccinated persons have developed immunity before the introduction of influenza A(H1N1) in the community.

Impact of timing and daily rate of vaccination

Under the scenario where vaccination of the recommended groups starts early so that the first vaccinated persons develop an immune response when the cumulative AR is 1%, the AR at the end of the epidemic is predicted to be 15.2%-19.9% for 2%-10% daily vaccination rates (Table 3). Initiating vaccination at a later stage of the epidemic (cumulative AR of 5%) would lead to moderate decreases in the total number of symptomatic cases that is not expected to decrease below 21% of the population, even with intensive daily vaccination rates (100 persons vaccinated daily/1,000 population). When the first vaccinated persons develop immunity near or at the peak of the epidemic (AR: 10% or 15%, respectively), the effectiveness of the intervention in reducing the number of symptomatic infections is estimated to be low (AR: 24.8%-28.5% and 27.8%-29.8%, respectively, for 2%-10% daily vaccination rates). Under the scenario of staged vaccination of the whole population, overall attack rates below 10% are anticipated only in the case where vaccination is initiated early in the epidemic (AR 1%) with intensive daily vaccination coverage (6%-10% of the population vaccinated/day) (Table 3).

Discussion

In the present study, mathematical modelling was used to evaluate the impact of vaccination strategies recommended by CDC's ACIP for pandemic influenza A(H1N1) as well as the impact of the timing of vaccination in a community typical of the European setting [3]. Vaccinating only the priority groups will have a negligible impact on the overall clinical attack rate. Vaccinating the groups recommended by CDC (i.e. priority groups and all children and young adults up to 24 years old) is predicted to be successful

Table 3

Impact of vaccination according to the timing of vaccination and to daily coverage during an ongoing epidemic (assuming up to 80% vaccination coverage of the target populations): A. Vaccination of recommended groups; B. Vaccination of the whole population.

		A. Vaccination of recommended groups			B. Staged vaccination of the whole population (first recommended groups, then individuals 25-64 years, then ≥65 years)		
		Attack rate (AR)	(% decrease)*	Number of cases prevented/ person vaccinated	Attack rate (AR)	(% decrease)*	Number of cases prevented/ person vaccinated
Before the epidemic (vaccinated individuals already immune when the epidemic starts)		9.6%	(72.2%)	0.86	2.5%	(92.8%)	0.40
During the epidemic							
The first vaccinated persons develop an immune response when the AR is:	Proportion of population vaccinated/day (%)						
1%	2%	19.9%	(42.3%)	0.57	17.0%	(50.7%)	0.26
	6%	15.7%	(54.5%)	0.70	8.8%	(74.5%)	0.34
	10%	15.2%	(55.9%)	0.72	7.3%	(78.8%)	0.36
5%	2%	26.2%	(24.1%)	0.38	25.5%	(26.1%)	0.16
	6%	22.8%	(33.9%)	0.47	16.9%	(51.0%)	0.25
	10%	21.7%	(37.1%)	0.50	15.3%	(55.7%)	0.26
10%	2%	28.5%	(17.4%)	0.31	28.2%	(18.3%)	0.12
	6%	26.2%	(24.1%)	0.36	23.2%	(32.8%)	0.17
	10%	24.8%	(28.1%)	0.42	20.6%	(40.3%)	0.20
15%	2%	29.8%	(13.6%)	0.27	29.2%	(15.4%)	0.11
	6%	28.3%	(18.0%)	0.30	26.2%	(24.1%)	0.14
	10%	27.8%	(19.4%)	0.32	24.6%	(28.7%)	0.15

*Compared to an AR of 34.5% in the absence of intervention

in mitigating the pandemic as it results in clinical attack rates below 10%, i.e. within the range of regular seasonal influenza (5%-15%). An additional advantage of this strategy is that it has significant indirect effects in the age groups that are not included in the target populations (i.e. individuals aged 25-64 and ≥65 years). Extending vaccination to include also individuals 25-64 years old is anticipated to result in very low attack rates of approximately 3%. However, once the demand for vaccine for these prioritised groups as well as for individuals 25-64 years old is met, offering vaccination to people over the age of 65 will not offer a notable additional benefit for this age group.

The above findings refer to the best-case scenario where vaccines are available before the onset of the epidemic in the population, such as e.g. in the case of countries of the northern hemisphere with still a small number of influenza A(H1N1) cases. When vaccination is implemented during the epidemic, its impact on the attack rate is predicted to be lower. Under intensive daily coverage, clinical attack rates of approximately 15% may be achieved by initiating vaccination either of the recommended groups early in the epidemic (AR 1%) or of the whole population somewhat later (AR 5%).

In the current analysis, we assumed that the pandemic evolves in a single wave whereas 2-3 waves have been observed in the majority of past pandemics [17,18]. As a result, although the model predicts modest to negligible reductions in the overall attack rate when vaccination is not introduced early during the ongoing epidemic, it might be used to abort the second and third waves [17]. Vaccination strategies were evaluated in a community with the structure of the Greek population (age and sex distribution, number and size of households etc). As a result, the quantitative results reported here are valid for Greece alone. However, due to the similarity in the age structure and household size of the Greek and the European population, results may apply qualitatively to other communities in the European region. A further point that requires caution is that the model was set up such as to simulate the age-specific attack rates of the pandemic influenza A(H1N1) outbreak in the community of La Gloria in Mexico. This particular outbreak provided very useful information as it evolved in the absence of intervention. However, the age-specific attack rates observed in the community of La Gloria might be considered as a worst-case assumption and the proportion of symptomatic infections that will be observed in European countries is likely to be smaller. A final point is that we did not deal explicitly with the time lag between vaccination and effectiveness and the partial efficacy between doses, in case multiple doses are required, but rather combined this delay time with that of production and distribution and refer only to the date at which vaccination becomes effective. Similarly, we have not estimated the number of doses needed to implement the various strategies but rather the number of vaccinated persons.

In conclusion, vaccinating the groups recommended by CDC's ACIP in countries with still a small number of pandemic influenza A(H1N1) cases is anticipated to reduce illness attack rates within the range of seasonal influenza (approximately 10%) with significant indirect effects among individuals older than 24 years who are not included in the target groups. For countries experiencing an ongoing epidemic, initiating vaccination of the recommended groups early might result in attack rates near the upper limit estimates of seasonal influenza.

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References

1. Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. Nature. 2006;442(7101):448-52.
2. Carrat F, Luong J, Lao H, Sallé AV, Lajaunie C, Wackernagel H. A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics. BMC Med. 2006;4:26.
3. Sypsa V, Hatzakis A. School closure is currently the main strategy to mitigate influenza A(H1N1)v: a modeling study. Euro Surveill. 2009;14(24):pii=19240. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19240
4. Halloran ME, Longini IM Jr, Struchiner CJ. Design and interpretation of vaccine field studies. Epidemiol Rev. 1999;21(1):73-88.
5. Allison MA, Daley MF, Crane LA, Barrow J, Beaty BL, Allred N, et al. Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003-2004 season. J Pediatr. 2006;149(6):755-62.
6. Hoberman A, Greenberg DP, Paradise JL, Rockette HE, Lave JR, Kearney DH, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. JAMA. 2003;290(12):1608-16.
7. Clover RD, Crawford S, Glezen WP, Taber LH, Matson CC, Couch RB. Comparison of heterotypic protection against influenza A/Taiwan/86 (H1N1) by attenuated and inactivated vaccines to A/Chile/83-like viruses. J Infect Dis. 1991;163(2):300-4.
8. Neuzil KM, Dupont WD, Wright PF, Edwards KM. Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. Pediatr Infect Dis J. 2001;20(8):733–40.
9. Zangwill KM, Belshe RB. Safety and efficacy of trivalent inactivated influenza vaccine in young children: a summary of the new era of routine vaccination. Pediatr Infect Dis J. 2004;23(3):189–97.
10. Bridges CB, Thompson WW, Meltzer MI, Reeve GR, Talamonti WJ, Cox NJ, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial. JAMA. 2000;284(13):1655-63.
11. Jefferson TO, Rivetti D, Di Pietrantonj C, Rivetti A, Demicheli V. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD001269.
12. Nichol KL, Lind A, Margolis KL, Murdoch M, McFadden R, Hauge M, et al. The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med. 1995;333(14):889-93.
13. Campbell DS, Rumley MH. Cost-effectiveness of the influenza vaccine in a healthy, working-age population. J Occup Environ Med. 1997;39(5):408–14.
14. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA. 1994;272(21):1661-5.
15. Basta NE, Halloran ME, Matrajt L, Longini IM Jr. Estimating influenza vaccine efficacy from challenge and community-based study data. Am J Epidemiol. 2008;168(12):1343-52.
16. CDC Advisory Committee on Immunization Practices. CDC Advisors Make Recommendations for Use of Vaccine Against Novel H1N1. 29 July 2009 [cited 28 August 2009]. Available from: http://www.cdc.gov/media/pressrel/2009/r090729b.htm.
17. Glezen WP. Emerging infections: pandemic influenza. Epidemiol Rev. 1996;18(1):64-76.
18. Taubenberger JK, Morens DM. Pandemic influenza--including a risk assessment of H5N1. Rev Sci Tech. 2009;28(1):187-202