



Information and Communication Technologies

## **Developing the Framework for an Epidemic Forecast Infrastructure**

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D4.5 Application of Epidemic Modelling Platform to seasonal influenza modeling in (i) participating countries; (ii) Europe; (iii) worldwide. Comparison with influenza surveillance data and harmonization of European countries preparedness plans on early and efficient responses to health emergencies

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## Change log

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## The epidemic modelling platform at work: the H1N1 case

### Introduction

The main research effort of the project is aimed at developing the appropriate framework of tools and knowledge needed for the design and implementation of modeling, computational and ICT tools to forecast epidemic scenarios with a high level of realism and based on data-driven computational models.

Key to the development of such an epidemic forecast infrastructure at the European level is a computational platform that can provide the access to the state-of-the-art modeling approaches to perform data-driven simulations of epidemic out-breaks. During the first three years of the project, to the development of a platform for the computational modeling of infectious disease spread has been designed, implemented and publicly released. The result is a publicly available software system, called “GLEAMviz” (<http://www.gleamviz.org>) that simulates the spread of emerging human-to-human infectious diseases across the world which is extensively described in the **Deliverable 4.4**. The approach of GLEAMviz is based on the balance of complex and sophisticated data-driven epidemic modeling at the global scale while maintaining an accessible computational speed and overall flexibility in the description of the simulation scenario, including the compartmental model, transition rates, intervention measures, and outbreak conditions by means of a user-friendly GUI. This software is a user-friendly tool for the simulation of a case study, test and validation of specific assumption on the spread of a disease, understanding of observed epidemic patterns, study of the effectiveness and results of different intervention strategies, analysis of risk through model scenarios, forecast of newly emerging infectious diseases.

As already mentioned in the Deliverable 4.4, the computational platform deployment and public releasing have been carried on in advance with respect to the planned scheduling because of the exceptional 2009 pandemic event, an opportunity that made the involved teams spend additional effort in the development of realistic modelling software. According to the Annex I, during the fourth year, the data-driven simulations had to be used for case studies analysis and epidemic forecasts on European and worldwide scale. Alongside the simulations at the national level, the project was supposed to address larger scale simulations, based on meta-population approaches – informed by agent based models at local community scale – at the European scale and at the worldwide level. On this respect, data gathered for the 2009 H1N1 influenza crisis represented an unprecedented opportunity to validate real-time model predictions and define the main success criteria for different approaches. The data gathered during the course of the pandemic have been used to compare with the estimates calculated by the models, representing an unprecedented opportunity to validate and assess the results obtained by computational and modeling approaches. Thus, during the fourth year, we assessed results obtained using the GLEAM computational model. With the emergence of the novel H1N1 virus in 2009, the model offered the opportunity to study the spread of the pandemic in real time, and thus evaluate specific public-health actions and provide stochastic forecasts of its future unfolding. The basic model parameters (transmissibility and seasonality) were obtained with a Monte Carlo Maximum Likelihood (MCML)-based approach using the chronological data on the pandemic invasion up to 18 June 2009 [2]. The work was done during the first year of the project. The obtained estimates were used to generate a large number of nominally identically initialized numerical stochastic simulations of the global progression of the H1N1 pandemic after 18 June 2009. The simulations provide, for each point in space and time as given by the resolution of the model, an ensemble of possible epidemic evolutions. It gives median, mean, and reference ranges for epidemic

observables, such as newly generated cases, seeding events, time of arrival of the infection, and number of drugs used. The ensemble forecast and the statistical quantities depend on the key parameters determined by the MCML calibration of the model. Each calibration thus defines a different stochastic forecast output (SFO) set that can be validated against real data. Thus, based on the early data of the H1N1 pandemic up to June 2009, the model allowed the stochastic forecasting of the activity peak of the fall/winter wave in the northern hemisphere, along with other quantities of interest. The forecasts were published in September 2009 [2], well before the peak weeks of epidemic activity in the northern hemisphere. The aim of the work carried out during the last year of the project and described in the present deliverable was to validate the model's predictions by comparing them with real-life data collected from surveillance and virologic sources in 48 countries in the northern hemisphere during the course of the pandemic. These data allowed independent validation of the obtained results and also allowed the accuracy of the model to be tested. Specifically, we considered the validity of the predicted peak time of the fall wave in the northern hemisphere and the effectiveness of vaccination. Furthermore, we analyzed results at a finer spatial resolution to ascertain the validity of the model on scales smaller than country level. Using the surveillance data, the timing of the pandemic activity peak was found to fall within the prediction interval for 87% of the countries. In the 13% of the cases falling outside the 95% reference range, the offset with respect to the confidence interval was, at most, 2 weeks at the country level. Because the activity peak in each country is defined as an average over regions composed of many different subpopulations, where data were available we have provided the analysis broken down into smaller surveillance regions, obtaining very good agreement between the model results and data. We also integrated into the model all available data on the vaccination campaigns in 27 countries, and compared the predicted incidence intervals with official estimates such as those produced by the Center for Disease Control and Prevention in the USA. In addition, we analyzed the effect of introducing into the model predictions a number of additional factors that were only known at the end of the pandemic, such as pre-existing immunity, and found that the epidemic timing results were sufficiently robust to cope with changes in these parameters.

This study shows that although supercomputing capabilities are required, data-driven MCM allows real-time forecasting of emerging influenza-like illnesses (ILIs) with an accuracy that can provide valuable information to inform public-health decision-making. The GLEAM computational tool also allows the introduction of further details in the population structure, such as age classes, and it has been aligned with an agent-based model [42], thus providing avenues for the development of hybrid computational approaches that are able to use different levels of data integration in different subpopulations, with an appropriate compromise between computational requirements and resolution scale of the results.

In the following we will report some of the most significant highlights of the work but all the details of this massive validation effort are reported in the paper:

Tizzoni M, Bajardi P, Poletto C, Ramasco JJ, Balcan D, Gonçalves B, Perra N, Colizza V, and Vespignani A,

**Real-time numerical forecast of global epidemic spreading: case study of 2009 A/H1N1pdm**

BMC Medicine 2012, 10:165

## Methods

We used the Global Epidemic and Mobility Model to generate stochastic simulations of epidemic spread worldwide, yielding (among other measures) the incidence and seeding events at a daily resolution for 3,362 subpopulations in 220 countries. Using a Monte Carlo Maximum Likelihood analysis, the model provided an estimate of the seasonal transmission potential during the early phase of the H1N1 pandemic and generated ensemble forecasts for the activity peaks in the northern hemisphere in the fall/winter wave. These results were validated against the real-life surveillance data collected in 48 countries, and their robustness assessed by focusing on 1) the peak timing of the pandemic; 2) the level of spatial resolution allowed by the model; and 3) the effectiveness of the vaccine.

### *1) Pandemic activity peaks in the northern hemisphere*

The influenza activity data collected from 48 countries in the northern hemisphere (some of which lie across the northern hemisphere and the Tropics region) showed that most of the countries experienced a single major influenza wave during the fall of 2009. Data from virus specimens collected worldwide indicated that the wave was mainly due to the 2009 A/H1N1 pandemic strain, which was the predominant strain in the 2009 to 2010 season, accounting for more than 90% of the sampled specimens [95]. The influenza activity in these countries peaked during the period October to December, much earlier than the usual timing of seasonal influenza for countries in the northern hemisphere, which generally ranges between January and March. The pandemic peaked first in North America between the end of September and the end of October (in Mexico first, then in the USA, and soon after in Canada), and later in Europe. The situation in Europe was more heterogeneous, leading to an overall range of timing for the week of peak activity from late October to late December. The peak timing from the surveillance data of the various countries was subdivided by world regions and ordered by timing within each region (Figure 5); with few exceptions, the first peak of activity was experienced by countries in Western Europe, later followed by Eastern Europe. Other countries in Asia, the Middle East, and North Africa were also analyzed, showing peak data in the months of November and December. We found that the peak week correlated significantly with the total air traffic of each individual country to and from North America, both in the data and in the model output (Table 4).

**Table 4 Correlation of population variables and epidemic statistics as seen and predicted by the model.**

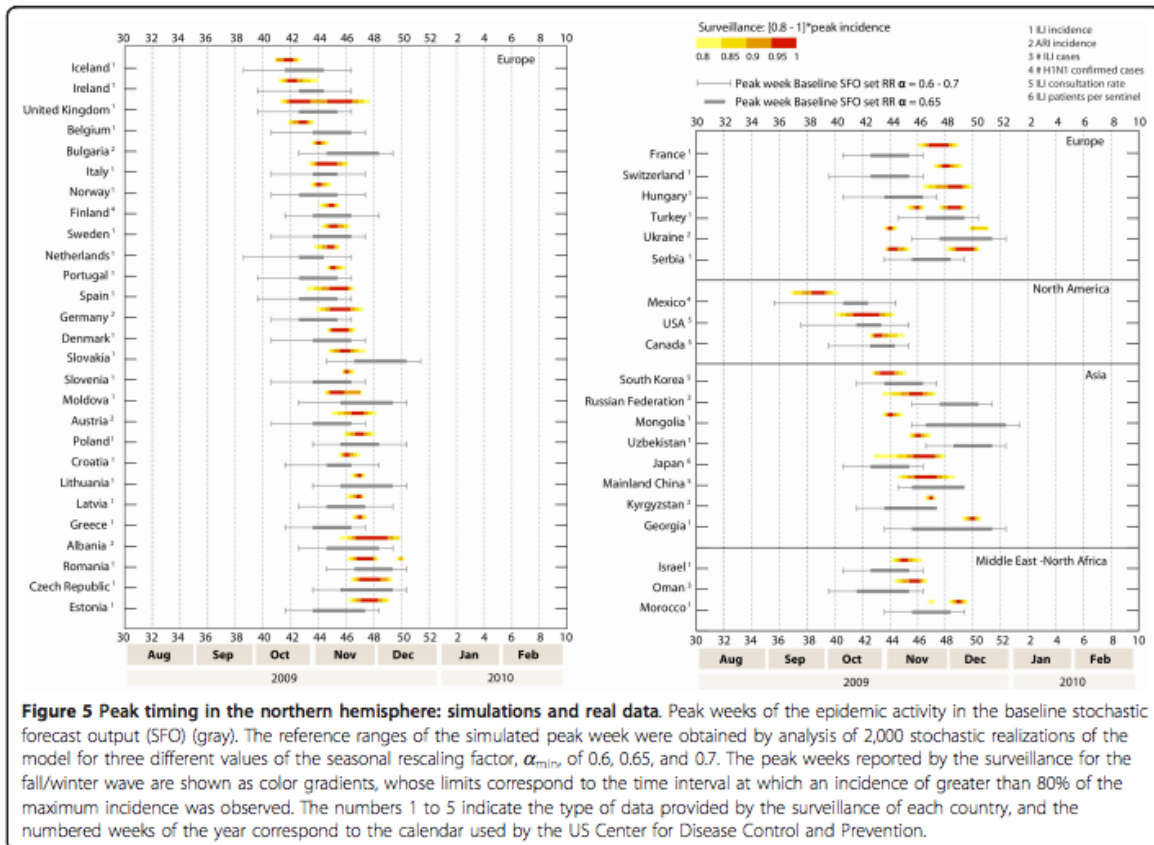
Full dataset					
Epidemic statistic	Population variable	Correlation observed in real data <sup>a</sup>		Correlation predicted by the model <sup>a</sup>	
		<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Worldwide					
Peak week	Air traffic to/from North America	-0.30	0.042	-0.30	0.044
Peak week	Longitude <sup>b</sup>	0.27	0.071	0.42	0.003
Peak week	Latitude <sup>b</sup>	-0.15	0.317	0.02	0.882
Peak week	Vaccine uptake	-0.37	0.069	-0.38	0.060
Attack rate reduction, %	Vaccine uptake			0.73	< 0.001
European countries only					
Peak week	Intra-EU air traffic	-0.15	0.391	-0.48	0.003
Peak week	Air traffic to/from North America	-0.26	0.151	-0.37	0.003
Peak week	Longitude <sup>b</sup>	0.54	< 0.001	0.74	< 0.001
Peak week	Latitude <sup>b</sup>	-0.32	0.07	-0.23	0.178
Peak week	Vaccine uptake	-0.29	0.204	-0.28	0.212
Attack rate reduction, %	Vaccine uptake			0.69	< 0.001

<sup>a</sup>Values of the Pearson's correlation coefficient, *r*, along with the corresponding *P* value, were measured between the epidemic statistics and the population variables of the countries appearing in Figure 5.

<sup>b</sup>Longitude and latitude are those of the capital city of the country.

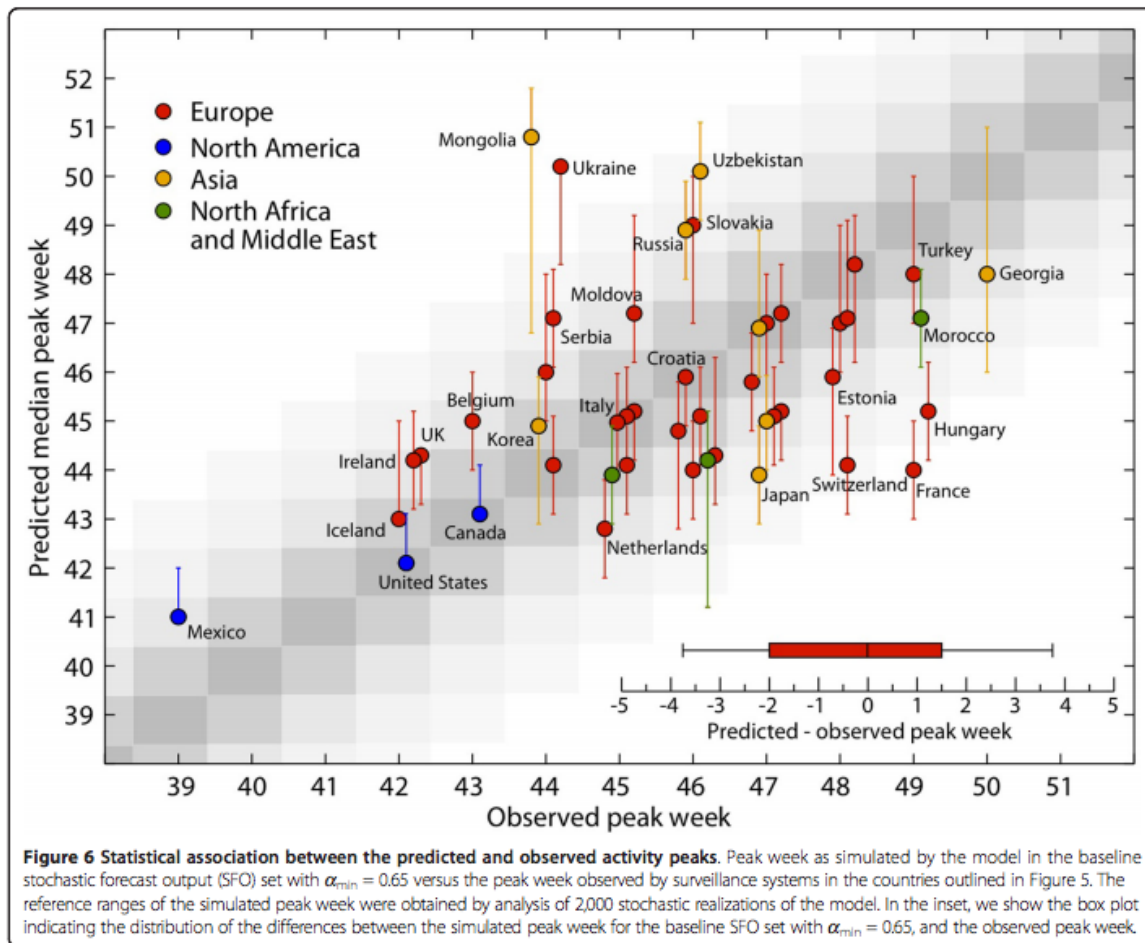
Similar correlations were found when we restricted the analysis to European countries, with a correlation between the peak week and the intra-European air traffic of any individual country, which was captured both by the data and the model. The peak week was also found to be positively correlated with a country's longitude, generally indicating a west to east pattern, and this correlation seemed to be stronger in Europe (as reported previously [39]), both in the data and the model output, probably as a result of the large air traffic between Western Europe and North America. A weak correlation was found between the peak week and the latitude of individual countries, both at the global level and when restricting the analysis to European countries.

The empirical data were compared with the results of the numerical simulations performed for the baseline SFO set (Figure 5).



We checked whether the timing of the simulated epidemic activity showed any differences between the reference SFO set (in which the observed travel drop during the early stage was incorporated into the model) and the baseline SFO set (in which that aspect was not considered because the data were not yet available), for which predictions were reported previously [1]. We found that 95% of the reference range of the simulated peak week was obtained from the minimal seasonality rescaling,  $\alpha_{\min}$ , in the range of 0.6 to 0.7, estimated from the calibration. The SFO sets therefore seemed to be in very good agreement with the empirical data, showing that the latter fell within the confidence interval of numerical results in most of the countries under study.

Only for 13% of the countries did our predictions differ from the observed timing of the influenza activity, and in these, the early arrival (France, Switzerland, Hungary) or the delay (Ukraine, Mongolia, Uzbekistan) compared with the simulations was 2 weeks at most, measured from peak week to the closest end value of the reference range of the numerical results. We compared the predicted peak week for the baseline SFO set with a  $\alpha_{\min} = 0.65$  against the observed peak week, and found a range of 4 weeks' difference (gray shaded area in Figure 6) between the observed and the predicted peak week. There was a significant correlation between the data and the prediction (Spearman correlation coefficient 0.48,  $P = 0.0001$ ). The error lay within 4 weeks for 95% of the countries, and within 2 weeks for 50% of them, and the median error was 0 (Figure 6).



We also compared the median predicted peak weeks and the observed peak weeks using the Wilcoxon signed-rank test, and found no significant difference between the two sets, at the 0.01 level of significance ( $Z$  score  $< 2.33$ ).

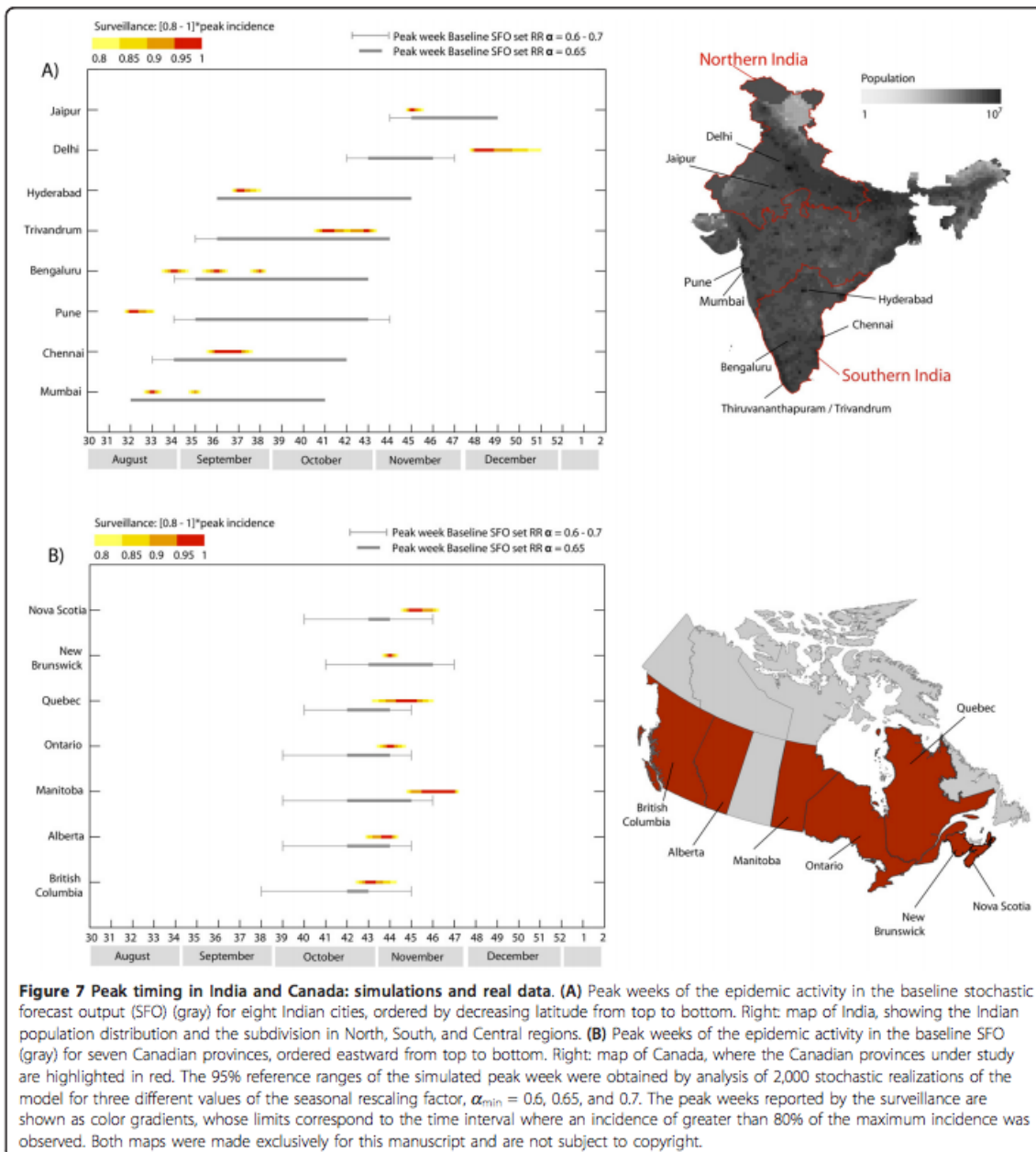
It should be noted that the obtained results are highly non-trivial because of the anticipated peak of the pandemic in the northern hemisphere. The GLEAM model does not alter the timing of the seasonal forcing that would intuitively generate an activity peak in mid-January. The anticipated peaks are thus a genuine result originating from the initial condition of the pandemic, the transmissibility estimate, and the spreading pattern generated by the human mobility integrated into the model. In this sense, the offset of 1 or 2 weeks observed for a limited number of countries can still be considered a good result, compared with the several months for dispersion allowed in principle by the seasonal forcing only.

An offset of 2 or 3 weeks for the forecast may be due not only to the model approximations and components but also to other factors that were not considered in the GLEAM model because of lack of data at the time of the predictions or because they would require country-specific implementation in the model. An example is provided by the case of France, where the beginning of the exponential increase of the incidence curve in fall 2009 was interrupted by a sudden drop [96], corresponding to a countrywide school break of 2 weeks (during weeks 43 and 44), consistent with the results observed from the analysis of the timing of holidays and from 21 years of French surveillance data of ILI [97]. The fact that the peak appeared 2 weeks later than predicted by the model may thus be explained by the delaying effect produced by the school holiday. This and other effects, although they could be implemented in the model through explicit or effective means, would require the collection of

country-specific data worldwide for a large spectrum of events. Although we performed simulations with explicit travel drops and vaccination campaigns at the country level as they took place in reality, the inclusion of country-specific additional factors, such as school holidays, were beyond the scope of this study. Calibration of GLEAM based on the chronological data of the H1N1 invasion up to 18 June 2009 was able to provide accurate predictions (2 to 4 months in advance) of the timing of the peak activity in countries in the northern hemisphere (Figure 5, Figure 6). This information provided additional support for the evaluation of real-time interventions aimed at mitigating the pandemic [68], and was made available to public-health policymakers to provide guidance for strategic planning. In addition, the large-scale extent of this approach enabled predictions for countries not usually considered by other modeling approaches that require large detailed datasets to build synthetic populations, and described their behavior at the individual level. Other than the USA [7,13,22,24,98], specific European countries [12,15], or the European continent as a whole [8], other developed countries do not appear in modeling studies, and underdeveloped countries have been considered in agent-based models in only a few cases, such as in pandemic preparedness studies that focused on Thailand with regard to the possible emergence of a pandemic from the H5N1 avian flu virus [11,24].

## *2) Spatial resolution analysis*

To test the reliability of the GLEAM model on a smaller geographical scale and in countries with heterogeneous climatic structures, we validated the baseline SFO for two countries, India and Canada, for which there are no specific models available and which are characterized by their large geographical extension. Furthermore, the coupling between the different regions of those countries is complicated by the presence of different seasonal areas within the same country (in the case of India) and by a highly structured population with a large extension of inhabited areas (in the case of Canada). We expected this to have a strong effect on the timing of the pandemic activity peak [9]. India is roughly halved by the Tropic of Cancer. Based on information from the Indian surveillance system, we identified three regions in the country: northern, southern, and central India (see map in Figure 7A).



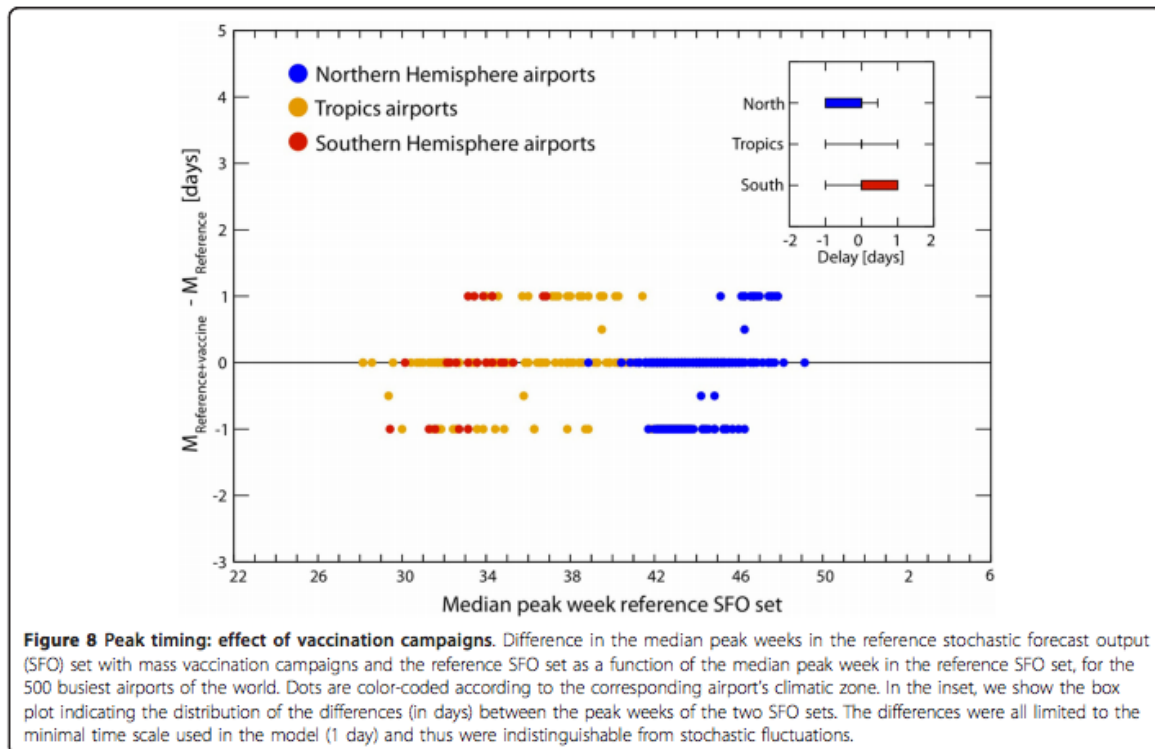
Northern India belongs to the northern hemisphere, where the seasonality rescaling function modulates the reproductive number, whereas southern India is a tropical region, where the reproductive number is fixed to its reference value  $R_0$ . Central India is crossed by the Tropic of Cancer, and therefore extends into both seasonal regions. Given this subdivision of the country into large regions, we examined in more detail the situation of eight large Indian cities for which influenza surveillance data were available. The pandemic wave peaked first in the cities in central and southern India, between August and October, whereas northern Indian cities experienced the activity peak later, in November and December (Figure 7A). Concerning the reference SFO results, the six cities in central and southern India are characterized by much wider reference ranges than those typically found for cities and countries in the northern hemisphere. This is due to the lack of seasonal forcing, which generally reduces stochastic effects and thus provides a smaller reference range for the SFO datasets. However, the timing reproduced by GLEAM simulations was able to capture the

early wave observed in central and southern India, which was then followed by the later peak of activity experienced in the cities of Jaipur and Delhi, which belong to the northern hemisphere. The SFO seems to indicate that the real mobility and population data integrated into the model are sufficient to provide useful information on the timing of the pandemic within the country, although the error bars for the results covered a duration of 4 to 6 weeks. At the national level, the aggregation of the pandemic waves experienced in the different regions at different times resulted in a double peak of the total incidence curve, as reported by the Indian surveillance system. In our reference SFO set, the incidence curve of India presented a double peak in more than 90% of the stochastic realizations of the model, reproducing the same seasonal pattern observed in reality. By contrast, Canada falls completely within the northern hemisphere, where the seasonal rescaling function modulates the value of  $R_0$ , leading to higher transmissibility rates during wintertime. The Canadian case is of interest because the country has one of the lowest population densities in the world, and is characterized by a largely heterogeneous geographical distribution, with cities mainly scattered along the border with the USA, and varying densities from west to east. Despite the synchronization effect of epidemic waves produced by seasonal rescaling, the heterogeneous population distribution in a vast area leaves room for an important role of the mobility pattern in shaping the timing of the arrival of the epidemic and its peak activity in different regions. We collected the weekly incidence data reported by the surveillance systems of seven Canadian provinces (Alberta, British Columbia, Manitoba, New Brunswick, Nova Scotia, Quebec, and Ontario, which account for more than 94% of the Canadian population), and compared the observed activity peak with the simulated peak in our baseline SFO. The pandemic activity peaked between the end of October and the end of November (weeks 43 to 47), with the timing over all regions spanning an entire month, and with the presence of narrow to broad peaks in the incidence profiles, as shown, for instance, by the cases of New Brunswick and Manitoba, respectively (Figure 7B). The 95% reference ranges of the peak week in our reference SFO simulations were in good agreement with the surveillance data, and were able to reproduce a variation in the timing of the peak occurrence across the country. This is a result of the interplay of the region's connection to the rest of the world where the epidemic was unfolding, and the intra-country connections and population distribution that drove the local epidemic propagation and internal coupling across regions due to local mobility. As expected, those regions that are better connected to the rest of the world through international travel flows of passengers experienced the peak earlier, with the exception of New Brunswick, which synchronized with the early timing of the peak; this may be explained by the large commuting flows from New Brunswick to the neighboring regions [3].

### *3) The effect of vaccination on peak timing*

Although generally implemented too late to affect the timing of the pandemic in the northern hemisphere, the reactive vaccination campaigns implemented by several countries in that region might have helped to accelerate the decline of the pandemic and reduce its final attack rate. We considered the data available for 2010 on the start and coverage of the vaccination campaigns in those countries in which this measure was implemented, in order to calculate the daily distribution of vaccines and provide a more realistic description of the interventions adopted worldwide. The final vaccine uptake differed widely between countries in the northern hemisphere, ranging from 0.6% of the population in the Czech Republic to about half of the population or more in the northern European countries (Sweden, Finland, Iceland,

Norway) and in Canada, thus resulting in a very heterogeneous picture. Notwithstanding the large uptakes reached in some countries, the effect of the mass vaccination campaigns on the timing of the epidemic was negligible, as would be anticipated in the case of an early peak scenario [68], because most of the vaccine doses were not deployed before November 2009. We integrated those data into the reference SFO dataset by generating a reference + vaccination dataset. We calculated the difference in the median value of the peak week between the reference + vaccination dataset and the reference SFO dataset for the 500 busiest transportation hubs worldwide and for a single seasonality value of a  $\alpha_{\min} = 0.65$  (Figure 8).



For all geographical locations, the difference in peak time between the reference + vaccination dataset and the reference SFO was no more than 1 day, with no significant changes in those countries with a larger fraction of immunized individuals. The real data and the model output provided similar results, as expressed in terms of a negative correlation, which was not significant, between the peak week and the vaccine uptake (Table 4), indicating a larger uptake in those countries that experienced an earlier pandemic wave, such as Canada and the USA.

## Conclusions

GLEAM is under continuous development and so far it has been used: to assess the role of short-range and long-range mobility in epidemic spread [3]; to retrospectively analyze the SARS outbreak of 2002-2003 in order to investigate the predictive power of the model [47]; to explore global health strategies for controlling an emerging influenza pandemic with pharmaceutical interventions under logistical constraints [5]; estimate the seasonal transmission potential of the 2009 H1N1 influenza pandemic during the early phase of the

outbreak to provide predictions for the activity peaks in the Northern Hemisphere [2]. In this final period of the project, we examined the application of GLEAM to the 2009 A/H1N1 pandemic in the scope of a broader validation effort. We analyzed, in real time, the pandemic emergency that led to the publication in summer 2009 of the predicted timing for the pandemic wave in the countries in the northern hemisphere for the fall/winter period. Using surveillance data from various monitoring and virologic sources, we have provided a validation of the SFO of the GLEAM model for the unfolding of the A/H1N1 pandemic in 2009. Our findings indicate very good agreement in the predicted timing for a large variety of countries, including those with underdeveloped surveillance schemes, and for intra-country spatial scales. The results are encouraging in advocating the use of large-scale computational approaches in providing real-time forecast and scenarios of epidemic outbreaks. If the appropriate MCML calibration is performed, the SFOs are very stable against changes in epidemiological parameters that are difficult to estimate for an emerging virus, such as the asymptomatic proportion of the population and its relative infectiousness. Changes in those parameters are generally absorbed by the rescaling of the key disease parameters in a self-consistent way. However, the model output shows strong dependence on the accuracy of the initial conditions and the mobility network considered. This highlights the need for a detailed level of description of human mobility and population distribution in the world in order to achieve reliable predictions at a high resolution scale. We also considered additional scenarios to allow more realistic simulation of the pandemic event worldwide, based on detailed data of country-based interventions and population initial immunity profiles, which became available throughout and after the outbreak. Consequently, accurate data should be rapidly available during the initial phase of the outbreak in order to allow careful calibration of the model, and close collaboration with public-health officials should allow careful consideration of possible intervention scenarios to support policy decisions for contingency planning at both country and global levels.

In the last months of the project, simulations of seasonal influenza in Europe have been carried out. These will further improve our understanding of the epidemic progression. Surveillance data collected by the WP5 Internet Monitoring System deployed in the various European countries are being used to initialize and train the GLEAM model parameters and data from the European Influenza Surveillance Network run by the ECDC will be used as a benchmark for the case study. Impacts of multi-scale community structure and effective geographic boundaries in Europe will be studied and tested in the simulations. This work is still in a very preliminary stage but looks very promising.

## References

1. Riley S: Large-scale transmission models of infectious disease. *Science* 2007, 316:1298-1301.
2. Balcan D, Hu H, Gonçalves B, Bajardi P, Poletto C, Ramasco JJ, Paolotti D, Perra N, Tizzoni M, Van den Broeck W, Colizza V, Vespignani A: Seasonal transmission potential and activity peaks of the new influenza A/H1N1: a Monte Carlo likelihood analysis based on human mobility. *BMC Med* 2009, 7:45.

3. Balcan D, Colizza V, Gonçalves B, Hu H, Ramasco JJ, Vespignani A: Multiscale mobility networks and the large scale spreading of infectious diseases. *Proc Natl Acad Sci USA* 2009, 106:21484-21489.
4. Grais RF, Hugh Ellis J, Glass GE: Assessing the impact of airline travel on the geographic spread of pandemic influenza. *Eur J Epidemiol* 2003, 18:1065-1072.
5. Colizza V, Barrat A, Barthélemy M, Valleron A-J, Vespignani A: Modeling the World-wide spread of pandemic influenza: baseline case and containment interventions. *PLoS Med* 2007, 4:e13.
6. Hufnagel L, Brockmann D, Geisel T: Forecast and control of epidemics in a globalized world. *Proc Natl Acad Sci USA* 2004, 101:15124-15129.
7. Eubank S, Guclu H, Kumar VSA, Marathe MV, Srinivasan A, Toroczkai Z, Wang N: Modeling disease outbreaks in realistic urban social networks. *Nature* 2004, 429:180-4.
8. Merler S, Ajelli M: The role of population heterogeneity and human mobility in the spread of pandemic influenza. *Proc R Soc B* 2009, 277:557-565.
9. Cooper BS, Pitman RJ, Edmunds WJ, Gay N: Delaying the international spread of pandemic influenza. *PLoS Med* 2006, 3:e12.
10. Ferguson NM, Keeling MJ, Edmunds WJ, Gani R, Grenfell BT, Anderson RM, Leach S: Planning for smallpox outbreaks. *Nature* 2003, 425:681-685.
11. Ferguson NM, Cummings DAT, Cauchemez S, Fraser C, Riley S, Meeyai A, Iamsirithaworn S, Burke DS: Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 2005, 437:209-214.
12. Ferguson NM, Cummings DAT, Fraser C, Cajka JC, Cooley PC, Burke DS: Strategies for mitigating an influenza pandemic. *Nature* 2006, 442:448-452.
13. Germann TC, Kadau K, Longini IM Jr, Macken CA: Mitigation strategies for pandemic influenza in the United States. *Proc Natl Acad Sci USA* 2006, 103:5935-5940.
14. Epstein J, Goedecke D, Yu F, Morris R, Wagener D, Bobashev G: Controlling pandemic flu: the value of international air travel restrictions. *PLoS One* 2007, 2:401.
15. Ciofi degli Atti ML, Merler S, Rizzo C, Ajelli M, Massari M, Manfredi P, Furlanello C, Scalia-Tomba G, Iannelli M: Mitigation measures for pandemic influenza in Italy: an individual based model considering different scenarios. *PLoS One* 2008, 3:e1790.
16. Hejblum G, Setbon M, Temime L, Lesieur S, Valleron A-J: Modelers' perception of mathematical modeling in epidemiology: a web-based survey. *PLoS One* 2011, 6:e16531.

17. Van Kerkhove MD, Asikainen T, Becker NG, Bjorge S, Desenclos JC, dos Santos T, Fraser C, Leung GM, Lipsitch M, Longini IM Jr, McBryde ES, Roth CE, Shay DK, Smith DJ, Wallinga J, White PJ, Ferguson NM, Riley S: Studies needed to address the public health challenges of the 2009 H1N1 influenza pandemic: insights from modeling. *PLoS Med* 2010, 7: e1000275.
18. Nishiura N: Prediction of pandemic influenza. *Eur J Epidemiol* 2011, 26:583-584.
19. Medlock J, Galvani A: Optimizing influenza vaccine distribution. *Science* 2009, 325:1705-1708.
20. Hollingsworth TD, Ferguson NM, Anderson RM: Will travel restrictions control the International spread of pandemic influenza? *Nature Med* 2006, 12:497-499.
21. Halloran ME, Ferguson NM, Eubank S, Longini IM, Cummings DAT, Lewis B, Xu S, Fraser C, Vullikanti A, Germann TC, Wagener D, Beckman R, Kadau K, Macken C, Burke DS, Cooley P: Modeling targeted layered containment of an influenza pandemic in the United States. *Proc Natl Acad Sci USA* 2008, 105:4639-44.
22. Flahault A, Vergu E, Coudeville L, Grais R: Strategies for containing a global influenza pandemic. *Vaccine* 2006, 24:6751-6755.
23. Longini IM Jr, Halloran ME, Nizam A, Yang Y: Containing pandemic influenza with antiviral agents. *Am J Epidemiol* 2004, 159:623-633.
24. Longini IM Jr, Nizam A, S X, Ungchusak K, Hanshaoworakul W, Cummings D, Halloran M: Containing pandemic influenza at the source. *Science* 2005, 309:1083-1087.
25. Bauch CT, Lloyd-Smith JO, Coffee MP, Galvani AP: Dynamically modeling SARS and other newly emerging respiratory illnesses: past, present, and future. *Epidemiology* 2005, 16:791-801.
26. Hall IM, Gani R, Hughes HE, Leach S: Real-time epidemic forecasting for pandemic influenza. *Epidemiol Infect* 2007, 135:372-385.
27. Fraser C, Donnelly C, Cauchemez S, Hanage W, Van Kerkhove M, Hollingsworth T, Griffin J, Baggaley R, Jenkins H, Lyons E, Jombart T, Hinsley W, Grassly N, Balloux F, Ghani A, Ferguson NM: Pandemic potential of a strain of influenza A/H1N1: early findings. *Science* 2009, 324:1557-1561.
28. Yang Y, Sugimoto JD, Halloran ME, Basta NE, Chao DL, Matrajt L, Potter G, Kenah E, Longini IM Jr: The transmissibility and control of pandemic influenza A/H1N1 virus. *Science* 2009, 326:729-733.
29. Flahault A, Vergu E, Boelle P-Y: Potential for a global dynamic of Influenza A (H1N1). *BMC Infect Dis* 2009, 9:129.

30. Boëlle PY, Bernillon P, Desenclos JC: A preliminary estimation of the reproduction ratio for new influenza A(H1N1) from the outbreak in Mexico, March-April 2009. *Euro Surveill* 2009, 14:19205.
31. Lipsitch M, Lajous M, O'Hagan J, Cohen T, Miller J, Goldstein E, Danon L, Wallinga J, Riley S, Dowell S, Reed C, McCarron M: Use of cumulative incidence of novel influenza A/H1N1 in foreign travelers to estimate lower bounds on cumulative incidence in Mexico. *PLoS One* 2009, 4: e6895.
32. White LF, Wallinga J, Finelli L, Reed C, Riley S, Lipsitch M, Pagano M: Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA. *Influenza Other Respi Viruses* 2009, 3:267-276.
33. Nishiura H, Castillo-Chavez C, Safan M, Chowell G: Transmission potential of the new influenza A(H1N1) virus and its age-specificity in Japan. *Euro Surveill* 2009, 14:19227.
34. Pourbohloul B, Ahued A, Davoudi B, Meza R, Meyers LA, Skowronski DM, Villaseñor I, Galván F, Cravioto P, Earn DJD, Dushoff J, Fisman D, Edmunds WJ, Hupert N, Scarpino SV, Trujillo J, Lutzow M, Morales J, Contreras A, Chávez C, Patrick DM, Brunham RC: Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. *Influenza Other Respi Viruses* 2009, 3:215-222.
35. Boni MF, Manh BH, Thai PQ, Farrar J, Hien TT, Hien NT, Van Kinh N, Horby P: Modelling the progression of pandemic influenza A (H1N1) in Vietnam and the opportunities for reassortment with other influenza viruses. *BMC Med* 2009, 7:43.
36. Nishiura H: Real-time forecasting of an epidemic using a discrete time stochastic model: a case study of pandemic influenza (H1N1-2009). *Biomed Eng Online* 2011, 10:15.
37. Ong JBS, Chen MI-C, Cook AR, Lee HC, Lee VJ, Pin Lin RT, Tambyah PA, Gan Goh L: Real-time epidemic monitoring and forecasting of H1N1-2009 using influenza-like illness from general practice and family doctor clinics in Singapore. *PLoS One* 2010, 5:e10036.
38. Baguelin M, van Hoeck AJ, Jit M, Flasche S, White PJ, Edmunds WJ: Vaccination against pandemic influenza A/H1N1v in England: A realtime economic evaluation. *Vaccine* 2010, 28:2370-2384.
39. Merler S, Ajelli M, Pugliese A, Ferguson NM: Determinants of the spatiotemporal dynamics of the 2009 H1N1 pandemic in Europe: implications for real-time modelling. *PLoS Comput Biol* 2011, 7:e1002205.
40. Kenah E, Chao DL, Matrajt L, Halloran ME, Longini IM Jr: The global transmission and control of influenza. *PLoS One* 2011, 6:e19515.
41. Bobashev G, Morris RJ, Goedecke M: Sampling for global epidemic models and the topology of an international airport network. *PLoS One* 2008, 3: e3154.

42. Ajelli M, Gonçalves B, Balcan D, Colizza V, Hu H, Ramasco JJ, Merler S, Vespignani A: Comparing large-scale computational approaches to epidemic modeling: agent-based versus structured metapopulation models. *BMC Infect Dis* 2010, 10:190.
43. Rvachev LA, Longini IM Jr: A mathematical model for the global spread of influenza. *Math Biosci* 1985, 75:3-22.
44. Viboud C, Bjornstad O, Smith D, Simonsen L, Miller M, Grenfell BT: Synchrony, waves, and spatial hierarchies in the spread of influenza. *Science* 2006, 312:447-451.
45. Flahault A, Valleron A-J: A Method for assessing the global spread of HIV-1 infection based on air travel. *Math Popul Stud* 1991, 3:1-11.
46. Colizza V, Barrat A, Barthélemy M, Vespignani A: The role of airline transportation network in the prediction and predictability of global epidemics. *Proc Natl Acad Sci USA* 2006, 103:2015-2020.
47. Colizza V, Barrat A, Barthélemy M, Vespignani A: Predictability and epidemic pathways in global outbreaks of infectious diseases: the SARS case study. *BMC Med* 2007, 5:34.
48. Coburn BJ, Bradley G, Wagner BG, Blower S: Modeling influenza epidemics and pandemics: insights into the future of swine flu (H1N1). *BMC Med* 2009, 7:30.
49. Balcan D, Gonçalves B, Hu H, Ramasco JJ, Colizza V, Vespignani A: Modeling the spatial spread of infectious diseases: The Global Epidemic and Mobility computational model. *J Computl Sci* 2010, 1:132-145.
50. SocioEconomic Data and Application Center at Columbia University: Gridded population of the world (GPW). [<http://sedac.ciesin.columbia.edu/gpw>].
51. International Air Transport Association. [<http://www.iata.org>].
52. Official Airline Guide. [<http://www.oag.com>].
53. Keeling MJ, Rohani P: Estimating spatial coupling in epidemiological systems: a mechanistic approach. *Ecol Lett* 2002, 5:20-29.
54. Sattenspiel L, Dietz K: A structured epidemic model incorporating geographic mobility among regions. *Math Biosci* 1995, 128:71-91.
55. Anderson RM, May RM: *Infectious Diseases of Humans: Dynamics and Control* Oxford University Press; 1992.
56. Carrat F, Vergu E, Ferguson NM, Lemaître M, Cauchemez S, Leach S, Valleron A-J: Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol* 2008, 167:775-785.
57. Gani J, D Jerwood D: Markov chain methods in chain binomial epidemic models. *Biometrics* 1971, 27:591-603.

58. Halloran ME, Longini IM Jr, Struchiner CJ: Binomial and stochastic transmission models. In. *Design and Analysis of Vaccine Studies, Statistics for Biology and Health* Springer, New York; 2010, 63-84.
59. GLEAMviz: The Global Epidemic and Mobility Model. [<http://www.gleamviz.org/simulator/>].
60. Van den Broeck W, Gioannini C, Goncalves B, Quaggiotto M, Colizza V, Vespignani A: The GLEAMviz computational tool, a publicly available software to explore realistic epidemic spreading scenarios at the global scale. *BMC Infect Dis* 2011, 11:37.
61. Basta NE, Halloran ME, Matrajt L, Longini IM: Estimating influenza vaccine efficacy from challenge and community-based study data. *Am J Epidemiol* 2008, 168:1343-1352.
62. Flahault A, de Lamballerie X, Hanslik T, Salez N: Symptomatic infections less frequent with H1N1pdm than with seasonal strains. *PLoS Curr Influenza* 2009, 1:RRN1140.
63. Bandaranayake D, Huang S, Bissielo A, Wood T: Seroprevalence of the 2009 A/H1N1 influenza pandemic in New Zealand. 2010 [<http://www.health.govt.nz/publication/seroprevalence-2009-influenza-h1n1-pandemicnew-zealand>].
64. Secretaria de Salud, Mexico: Brote de infeccion respiratoria aguda en La Gloria, Municipio de Perote, Mexico, 2009. [<http://portal.salud.gob.mx/contenidos/noticias/influenza/estadisticas.html>].
65. Lipsitch M, Hayden FG, Cowling BJ, Leung GM: How to maintain surveillance for novel influenza A H1N1 when there are too many cases to count. *Lancet* 2009, 374:1209-1211.
66. Colizza V, Vespignani A, Perra N, Poletto C, Goncalves B, Hu H, Balcan D, Paolotti D, Van den Broeck W, Tizzoni M, Bajardi P, Ramasco JJ: Estimate of novel influenza A/H1N1 cases in Mexico at the early stage of the pandemic with a spatially structured epidemic model. *PLoS Curr Influenza* 2009, 1:RRN1129, doi:10.1371/currents.RRN1129.
67. Indiana University Pervasive Technology Institute: High performance systems. [<http://www.sct.gob.mx>].
68. Bajardi P, Poletto C, Balcan D, Hu H, Goncalves B, Ramasco JJ, Paolotti D, Perra N, Tizzoni M, Van den Broeck W, Colizza V, Vespignani A: Modeling vaccination campaigns and the Fall/Winter 2009 activity of the new A/H1N1 influenza in the Northern Hemisphere. *EHT Journal* 2009, 2:e11.
69. Girard MP, Tam JS, Assossou OM, Kieny MP: The 2009 A (H1N1) influenza virus pandemic: A review. *Vaccines* 2010, 28:4895-4902.
70. Ghani AC, Donnelly CA, Cox DR, Griffin JT, Fraser C, Lam TH, Ho LM, Chan WS, Anderson RM, Hedley AJ, Leung GM: Methods for estimating the case fatality ratio for a novel, emerging infectious disease. *Am J Epidemiol* 2005, 162:479-86.

71. Arinaminpathy N, McLean AR: Antiviral treatment for the control of pandemic influenza: some logistical constraints. *J R Soc Interface* 2008, 5:545-53.
72. Wu JT, Riley S, Fraser C, Leung GM: Reducing the impact of the next influenza pandemic using household-based public health interventions. *PLoS Med* 2006, 3:e361.
73. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012, 1:CD008965.
74. Singer AC, Howard BM, Johnson AC, Knowles CJ, Jackman S, Accinelli C, Caracciolo AB, Bernard I, Bird S, Boucard T, Boxall A, Brian JV, Cartmell E, Chubb C, Churchley J, Costigan S, Crane M, Dempsey MJ, Dorrington B, Ellor B, Fick J, Holmes J, Hutchinson T, Karcher F, Kelleher SL, Marsden P, Noone G, Nunn MA, Oxford J, Rachwal T, et al: Meeting report: risk assessment of Tamiflu use under pandemic conditions. *Environ Health Perspect* 2008, 116:1563-1567.
75. Mexican Secretaría de Comunicaciones y Transportes: Boletín Mensual de Estadística Operacional de la Aviación Civil en México. [[http://www.sct.gob.mx/uploads/media/BO\\_DICIEMBRE\\_09.pdf](http://www.sct.gob.mx/uploads/media/BO_DICIEMBRE_09.pdf)].
76. Bajardi P, Poletto C, Ramasco JJ, Tizzoni M, Colizza V, Vespignani A: Human mobility networks, travel restrictions and the global spread of 2009 H1N1 pandemic. *PLoS One* 2011, 6:e16591.
77. Cruz-Pacheco G, Duran L, Esteva L, Minzoni A, López-Cervantes M, Panayotaros P, Ahued A, Villaseñor I: Modelling of the influenza A/H1N1v outbreak in Mexico City, April-May 2009, with control sanitary measures. *Euro Surveill* 2009, 14:19254.
78. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M: Incidence of 2009 pandemic A H1N1 infection in England: a crossserological study. *Lancet* 2010, 375:1100-1108.
79. Ikonen N, Strengell M, Kinnunen L, Osterlund P, Pirhonen J, Broman M, Davidkin I, Ziegler T, Julkunen I: High frequency of cross-reacting antibodies against 2009 pandemic influenza A(H1N1) virus among the elderly in Finland. *Euro Surveill* 2010, 15:19478.
80. Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, Liu F, Dong L, DeVos JR, Gargiullo PM, Brammer TL, Cox NJ, Tumpey TM, Katz JM: Crossreactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med* 2009, 361:1945-1952.
81. Allwinn R, Geiler J, Berger A, Cinatl J, Doer HW: Determination of serum antibodies against swine-origin influenza A virus H1N1/09 by immunofluorescence, haemagglutination inhibition, and by neutralization tests: how is the prevalence rate of protecting antibodies in humans? *Med Microbiol Immunol* 2010, 199:117-121.
82. Leung GM, Nicoll A: Reflections on Pandemic (H1N1) 2009 and the international response. *PLoS Med* 2010, 7:e1000346.

83. U.Census: International programs. [<http://www.census.gov/ipc/www/idb/>].
84. United Kingdom Health Protection Agency: Swine influenza case definition. [[http://www.see.nhs.uk/content/file/GP\\_Zone/HPAcasedefinitionforswineflu.pdf](http://www.see.nhs.uk/content/file/GP_Zone/HPAcasedefinitionforswineflu.pdf)].
85. US Center for Disease Control: Case definition for influenza A (H1N1) virus infection. [[http://www.medicalcriteria.com/site/index.php?option=com\\_content&view=article&id=251%3Ainfh1n1&catid=59%3Ainfectious-disease&Itemid=80&lang=en](http://www.medicalcriteria.com/site/index.php?option=com_content&view=article&id=251%3Ainfh1n1&catid=59%3Ainfectious-disease&Itemid=80&lang=en)].
86. Aguilera JF, Paget WJ, Mosnier A, Heijnen ML, Uphoff H, van der Velden J, Vega T, Watson JM: Heterogeneous case definitions used for the surveillance of influenza in Europe. *Euro J Epidemiol* 2003, 18:751-754.
87. Paget J, Marquet R, Meijer A, van der Velden K: Influenza activity in Europe during eight seasons (1999-2007): an evaluation of the indicators used to measure activity and an assessment of the timing, length and course of peak activity (spread) across Europe. *BMC Infect Dis* 2007, 7:141.
88. Influenzanet. EPIWORK. [<http://www.epiwork.eu>].
89. Brooks-Pollock E, Edmunds WJ, Eames KTD: Using an online survey of healthcare-seeking behaviour to estimate the magnitude and severity of the 2009 H1N1v influenza epidemic in England. *BMC Infect Dis* 2011, 11:68.
90. Fleming DM: Influenza surveillance, the swine-flu pandemic, and the importance of virology. *Clin Evid* 2009 [<http://clinicalevidence.bmj.com/downloads/16-11-09.pdf>].
91. van Hoek AJ, Miller E: Response to guest editorial “Influenza surveillance, the swine-flu pandemic, and the importance of virology”. *Clin Evid* 2010 [<http://clinicalevidence.bmj.com/cweb/resources/editors-letter-response.jsp>].
92. Scalia Tomba G, Wallinga J: A simple explanation for the low impact of border control as a countermeasure to the spread of an infectious disease. *Math Biosci* 2008, 214:70-72.
93. Cowling BJ, Lau LL, Wu P, Wong HW, Fang VJ, Riley S, Nishiura H: Entry screening to delay local transmission of 2009 pandemic influenza A (H1N1). *BMC Infect Dis* 2010, 10:82.
94. Colizza V, Vespignani A: Epidemic modeling in metapopulation systems with heterogeneous coupling pattern: theory and simulations. *J Theor Biol* 2008, 251:450-467.
95. World Health Organization: Pandemic H1N1 2009. [<http://www.who.int/csr/disease/swineflu/en/>].
96. Réseau Sentinelles France, INSERM, UPMC, Institut de Veille Sanitaire. [<http://websenti.u707.jussieu.fr/sentiweb/>].
97. Cauchemez S, Valleron AJ, Boelle PY, Flahault A, Ferguson NM: Estimating the impact of school closure on influenza transmission from Sentinel data. *Nature* 2008, 452:750-54.

98. Chao DL, Halloran ME, Obenchain VJ, Longini IM Jr: FluTE, a publicly available stochastic influenza epidemic simulation model. *PloS Comput Biol* 2010, 6:e1000656.
99. World Health Organization: Seroepidemiological studies of pandemic influenza A(H1N1) 2009 virus. *Wkly Epidemiol Rec* 85 2010, 24:229-236.
100. Carrat F, Pelat C, Levy-Bruhl D, Bonmarin I, Lapidus N: Planning for the next influenza H1N1 season: a modelling study. *BMC Infecti Dis* 2010, 10:301.
101. US Center for Disease Control and Prevention: Updated CDC Estimates of 2009 H1N1 influenza cases, hospitalizations and deaths in the United States, April 2009-April 10, 2010. [[http://www.cdc.gov/h1n1flu/estimates\\_2009\\_h1n1.htm](http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm)].
102. Baguelin M, Hoschler K, Stanford E, Waight P, Hardelid P, Andrews N, Miller E: Age-specific incidence of A/H1N1 2009 influenza infection in England from sequential antibody prevalence data using likelihoodbased estimation. *PLoS One* 2011, 6:e17074.
103. Ross T, Zimmer S, Burke D, Crevar C, Carter D, Stark J, Giles B, Zimmerman R, Ostroff S, Lee B: Seroprevalence Following the Second Wave of Pandemic 2009 H1N1 Influenza. *PLoS Curr Influenza* 2010, 1:RRN1148.
104. Wu JT, Ma ES, Lee CK, Chu DK, Ho PL, Shen AL, Ho A, Hung IF, Riley S, Ho LM, Lin CK, Tsang T, Lo SV, Lau YL, Leung GM, Cowling BJ, Malik Peiris JS: The infection attack rate and severity of 2009 pandemic H1N1 influenza in Hong Kong. *Clin Infect Dis* 2010, 51:1184.
105. Chao DL, Matrajt L, Basta NE, Sugimoto JD, Dean B, Bagwell DA, Ojulfstad B, Halloran ME, Longini IM Jr: Planning for the control of pandemic influenza A(H1N1) in Los Angeles County and the United States. *Pract Epidemiol* 2011, doi:10.1093/aje/kwq497.
106. Ajelli M, Merler S, Pugliese A, Rizzo C: Model predictions and evaluation of possible control strategies for the 2009 A/H1N1v influenza pandemic in Italy. *Epidemiol Infect* 2011, 139:68.
107. Nishiura H, Chowell G, Castillo-Chavez C: Did modeling overestimate the transmission potential of pandemic (H1N1-2009)? Sample size estimation for post-epidemic seroepidemiological studies. *PLoS One* 2011, 6:e17908.
108. Grais RF, Eliis JH, Kress A, Glass GE: Modeling the spread of annual influenza epidemics in the U.S.: The potential role of air travel. *Health Care Manag Sci* 2004, 7:127.2222