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► **To cite this version:**

Antoine Nougairède, Rémi N. Charrel, Didier Raoult. Models cannot predict future outbreaks: A/H1N1 virus, the paradigm. *European Journal of Epidemiology*, 2010, 26 (3), pp.183-186. 10.1007/s10654-010-9533-6 . hal-00651656

HAL Id: hal-00651656

<https://hal.science/hal-00651656>

Submitted on 14 Dec 2011

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1 **Models cannot predict future outbreaks: A/H1N1 virus, the paradigm**

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20 **Key Words:** pandemic, model, Influenza, prediction, outbreak, H1N1

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22 **Abstract**

23 Evolution of the industrialized society had led to a risk management policy in many domains.
24 Assessment of health care risk in the case of infectious diseases often includes mathematical
25 models. Results of modelling were used in France to design emergency plans against flu
26 pandemic. We believe that models cannot predict the features of the future outbreaks
27 because the intrinsic properties of an emergent pathogen and the ecosystem in which it is
28 developing are very complex. Of course, prediction of future outbreaks is not possible
29 without using models, but we think that it is an illusion to presently believe that emerging
30 phenomenon can be anticipated by using only prediction from models. The recent pandemic
31 caused by the novel A/H1N1 virus has confirmed the unpredictability of infectious diseases.
32 The rapid evolution in several domains such as antimicrobial therapeutics, vaccine and
33 hygiene conditions make comparison with past pandemics hard. The adherence of
34 populations to prevention measures and immunisation campaigns are unpredictable. In
35 addition, the presentation of pessimistic models is deleterious. They impress governments
36 and provoke fears. There is a striking necessity to develop the number and the capacities of
37 sentinel centres to take and adapt decisions based on timely available scientific information.

38

39 Evolution of society had led to a risk management policy in many domains. The
40 assessment of health care risk in infectious diseases, especially concerning future epidemics,
41 often includes mathematical models which tentatively predict *in silico* the burden of the
42 future outbreaks such as attack rate, dissemination, morbidity or mortality. Currently,
43 models are designed to run with different scenarios, and probabilistic methods allow testing
44 their performance in a number of situation. But the question asked by physicians, scientists
45 and in fact everyone is “how many people will die, how many will be hospitalized?”. Such
46 predictions from models were used in France to design the emergency plan against flu
47 pandemic [1]. We believe that models cannot predict with acceptable accuracy the features
48 of the future outbreaks because the intrinsic properties of an emergent pathogen and the
49 ecosystem in which it is developing are very complex and unstable. Of course, prediction of
50 future outbreaks is not possible without using models, but we think that it is an illusion to
51 presently believe that emerging phenomenon can be anticipated by using only prediction
52 from models. The recent pandemic caused by the novel A/H1N1 virus has confirmed the
53 unpredictability of infectious diseases.

54 Seasonality of respiratory infections is a well-known phenomenon in temperate
55 regions. Flu has long been associated with cold season, and the word "Influenza" comes
56 from “influenza di freddo” in Italian that means “cold influenced”. A marked peak of
57 respiratory infections occurs during cold winter months. Several mechanisms have been
58 proposed to explain it, such as seasonal environmental changes (temperature humidity...),
59 seasonal host-behaviour changes and seasonal changes in host physiology (melatonin,
60 vitamin D...) [2-4]. However there is still no clear understanding of this phenomenon. In
61 contrast, disease seasonality is less defined in tropical regions where a background of
62 influenza cases is observed throughout the year on top of which epidemics occur at
63 intermediate months between the influenza season in temperate countries of the Northern
64 and Southern hemispheres [4]. On the top, none of yet proposed determinants can explain
65 why the four last pandemics of influenza (1918, 1957, 1968, and 2009) did not initiate during
66 the cold season.

67 Interference between several respiratory viruses affecting the spread of influenza
68 was recently described in Europe and drastically modified the dynamics of the outbreak [5-
69 6]. In France and in Sweden, an epidemic of rhinovirus infections occurred after the start of

70 school year, and delayed the onset of the A/H1N1 pandemic. We also observed in Marseille
71 that the epidemic of Respiratory Syncytial Virus bronchiolitis, which happens usually just
72 before the seasonal flu epidemic, occurred later in the season, just after that the A/H1N1
73 pandemic started to decline. In addition interference between several Influenza viruses
74 remains not properly known: at the beginning of the A/H1N1 pandemic, nobody was able to
75 predict whether seasonal influenza strains (H3N2 and H1N1) would still provoke an epidemic
76 wave or not.

77 In certain groups of population, the presence of cross-reactive antibodies against a
78 new pandemic strain of influenza can heavily affect viral dissemination and therefore impact
79 on the epidemiologic characteristics of the pandemic (total number of cases, age of the
80 cases, number of severe cases, number of deaths, death rate, length of the phenomenon...)
81 and seems unpredictable. The fact that the elderly were partially protected against the novel
82 A/H1N1 [7-9] explains that the novel A/H1N1 virus infected mostly young people. In
83 addition, at-risk groups may not be the same as for seasonal flu. For example, obesity was an
84 undisputable independent risk factor of severity and lethality during the A/H1N1 pandemic
85 [10-11].

86 The inherent variability of new variants makes predictions difficult. Each pandemic
87 virus has its own intrinsic properties which can evolve during the pandemic period. Then,
88 intrinsic pathogenicity of new pandemic variants appears to be unpredictable. Data
89 experimental derived from animal models must not be directly extrapolated to humans: in
90 the A/H1N1 case, experiences with ferrets predicted a severity of pneumonia intermediate
91 between that due to seasonal virus and the highly pathogenic avian H5N1 virus [12]. But in
92 fact, the fatality rate of the novel A/H1N1 virus was relatively mild.

93 The novel 2009 H1N1 virus reminded the 1918 pandemic, also caused by a H1N1
94 virus, despite totally distinct, which was associated with a large number of secondary
95 bacterial co-infection which could explain partially the huge number of deaths [13]. Because
96 of drastically different sanitary conditions nowadays, it is awkward to use the 1918 data as a
97 basis for anticipating the spread, severity, and health consequences of present and future
98 H1N1 pandemics. Currently, the use of antibiotics and anti-pneumococcal vaccines allow to
99 efficiently combat the historically lethal bacterial co-infections. The availability of adapted
100 vaccine and the rapid evolution on several domains such as antiviral therapeutics and

101 hygiene conditions are likely to play a critical role in the burden of these new pandemic
102 variants as well as the increase of air traffic in their spread. Some models take into account
103 the impact of human interventions such as vaccine/antiviral delivery, isolation of infected
104 patients, school closure, halting air traffic and non-pharmaceutical interventions. Moreover,
105 it remains often difficult to evaluate their real impact even without applying any model. For
106 example, it was only in the late nineties that hand washing indisputably demonstrated,
107 through randomized trials, its efficacy to prevent inter-human transmission in developed
108 countries [14-15]. In 2005, a randomized-trial in Pakistan confirmed it in low-income
109 countries [16]. Furthermore, the efficacy of mask use, largely recommended during A/H1N1
110 pandemic, to prevent respiratory infections is still to be clearly established by randomized
111 trials [17-19]. Thereby, their introduction into models seems very tricky.

112 The vast majority of studies showed that immunization against influenza has a true
113 impact in terms of hospitalization rate, global morbidity, influenza associated mortality as
114 well as global mortality [20-26]. Intriguingly, during the immunisation campaign against the
115 A/H1N1 pandemic virus, a large proportion of the population was reluctant to accept
116 vaccination in some countries such as France and Germany. Human behaviours often are
117 unpredictable and could vary among countries and vary with time. In France, the negative
118 image provided by the mass media could have contributed to the low uptake of the A/H1N1
119 vaccine. We observed and reported that in public hospitals of Marseille, the nurses were less
120 immunised against the new A/H1N1 pandemic virus than against seasonal flu [27]. Fears of
121 vaccination promoted by anti-immunization lobbies are largely relayed by the media and the
122 doubts induced and amplified by mediatisation persists for a long time, even when scientists
123 have demonstrated that there is no scientific evidence for suspicion. The association
124 between multiple sclerosis and hepatitis B vaccine on one hand [28], and between autism
125 and measles vaccine on the other hand [29] will be standing for many years to come, and
126 any model is able to predict these events. One model can predict the willingness to accept a
127 vaccine only for one specific situation. External factors cannot be included into models
128 because they are often unknown until they appear. In France, the fact that medical
129 information about the A/H1N1 vaccine was delivered and promoted primarily by politicians
130 could have a counterproductive effect. Medical recommendations bypassing the medical
131 system arouse suspicion in the population [27].

132 With hindsight, the recent pandemic reinforces the idea that presentation of
133 pessimistic models mostly based on extrapolated hypotheses is deleterious. They impress
134 governments and provoke fears. In another hand, it has been previously observed that
135 pessimistic hypothesis about bioterrorism based only on speculations led governments to
136 elaborate countermeasure plans with disproportionate measures. The Dark Winter
137 operation, a bio-terrorist attack simulation, resembles movie script more than reality. Fears
138 of a putative H5N1 avian flu pandemic amplified by pessimistic figures based on
139 unsupported prediction constrained governments to implement emergency flu plans. Later
140 on, these plans postulated that the fatality rate will be close to that observed in cases of
141 A/H5N1 infection. For example, In France the 2009 emergency plan against pandemic flu
142 predicted 91 000 to 212 000 deaths [1]. But A/H5N1 virus is still an almost pure zoonotic
143 agent with transmission properties drastically distinct from those of the human adapted
144 H1N1, H2N2 or H3N2 viruses. During the A/H1N1 pandemic in Marseille, no intermediate
145 measure had been planified between (i) maintaining the organisation and logistics of the
146 public hospital system as it was before the crisis, and (ii) the emergency opening of a 700
147 bed-hospital exclusively dedicated for A/H1N1 infected patients. In the real-life situation,
148 along 10 month pandemic period, more than 2,500 clinical specimens were laboratory-
149 documented: of these patients, around 11% were hospitalized and used simultaneously less
150 than 50 beds at the peak of the pandemic.

151 In conclusion, infectious diseases remain unpredictable with mathematical models
152 because pathogens and their ecosystem evolve continuously in a very unstable manner. Of
153 course, some models which take into consideration the antiviral/antimicrobial therapies, the
154 vaccines, the sanitary condition and the non-pharmaceutical interventions are useful to
155 anticipate some logistic problems (quantity to purchase...) and can help to prepare the
156 response to the future pandemics but they cannot predict with acceptable accuracy the
157 major features of a future pandemic (number of cases, hospitalization, deaths...). The
158 pessimistic predictions resulting from bioterrorism and the putative avian flu outbreak were
159 published in highly-rated scientific journals. However they were neither supported by
160 indisputable scientific evidence nor confirmed in real-time up to now. They fuelled fears in
161 the population through amplification by the media, causing great concern amongst the
162 public and the politicians. In order to fight future outbreaks and as a complementary

163 approach of modelling methods, we need to reinforce the network of sentinel centres by
164 increasing their timely detection/diagnostics capacities and by implementing a large variety
165 of technological tools detecting abnormal events. The data from these sentinel centres
166 should not be necessarily exhaustive but they require to produce sufficient amount of data
167 to investigate emergence and epidemic tendencies. Coupled with the fact that data from
168 hospital-based surveillance systems and Google searching tools are easily and timely
169 available, such surveillance method system will not be very costly. Our capacity for analysis
170 and laboratory documentation needs to be increased and better integrated; during a crisis
171 all data must be rapidly shared using communication media such as internet [30]. Rapid
172 communication of research using specific free media such as Promed and 'PloS Currents:
173 Influenza' can also improve the information dissemination. In addition, very early data about
174 a new variant could be incorporate in some models and then produce more accurate
175 predictions. Furthermore, decision process should be based on timely available scientific
176 data to allow decision makers to take real time decision. Precautionary principle should be
177 advantageously replaced by alertness principle.

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