Influenza vaccination: from epidemiological aspects and advances in research to dissent and vaccination policies

R. GASPARINI, D. AMICIZIA, P.L. LAI, D. PANATTO
Department of Health Sciences, University of Genoa, Italy

Keywords

Influenza • Influenza vaccine • Dissent

Summary

Influenza is a serious public health problem, since seasonal epidemics affect approximately 5-10% of the population and thus give rise to a heavy social and healthcare burden. The heavy burden of disease is due to several factors, one of which is the biological features of the pathogen. Indeed influenza viruses display high mutation rates and undergo frequent genetic reassortment. Minor variations cause seasonal epidemics and major variations, which result from the hybridization of viruses typical of different animal species, can lead to pandemics.

Vaccination remains the most efficacious means of mitigating the harmful healthcare and social effects of influenza. Influenza vaccines have evolved over time in order to offer broader protection against circulating strains. Trivalent vaccines containing two A viruses and one B virus are currently available. However, given the co-circulation of both B virus lineages (B/Yamagata and B/Victoria), quadrivalent vaccines have recently been developed. The new quadrivalent vaccines constitute a great advance, in that they can offer broader strain coverage.

Despite the availability of effective and safe influenza vaccines, the Italian public's trust in vaccination has declined and, in the last few years, influenza vaccination coverage rates have decreased both among the elderly and among at-risk adults. It is therefore necessary that users, in their own interests, regain trust in this important means of disease prevention.

In order to mitigate the damage wreaked by influenza, it seems important to: (i) improve clinical-epidemiological and virological surveillance of the disease; (ii) promote the development of new efficacious vaccines, as has recently been done through the introduction of the quadrivalent vaccine; (iii) extend free vaccination to the entire population, as in the US and Canada; (iv) ensure that general healthcare professionals are properly informed and always updated with regard to vaccination; (v) promote public campaigns to raise the population's awareness of the importance of vaccination; (vi) inform politicians and other decision-makers of scientific results in the field of vaccination; (vii) fight the anti-vaccination lobbies with every available weapon.

Influenza, which is caused by the homonymous virus belonging to the *Orthomyxoviridae* family, is a disease characterized by fever, respiratory and other systemic symptoms. In both the northern and southern hemispheres, the disease occurs annually, during the cold season (seasonal influenza). Periodically – at intervals of 20-30 years – antigenically new viruses may appear and cause a pandemic [1].

Influenza is a serious public health problem, since seasonal epidemics affect approximately 5-10% of the population and thus give rise to a heavy social and healthcare burden. Influenza-related direct costs are very high and mostly linked to severe disease complications and deaths, which are usually observed among at-risk subjects (elderly, subjects with chronic diseases and pregnant women). Moreover, a typical epidemic peak is associated with high rates of absenteeism, which, from the societal point of view, cause a heavy economic burden and hamper public services, especially those offered by the National Health System [1].

The heavy burden of disease is due to several factors, one of which is the biological feature of the pathogen. Indeed, the biology of the influenza virus is complex and conditions the epidemiology of the disease. Three types of virus are known: A, B and C. While types A and C can infect man and many animal species, B viruses almost exclusively infect humans [2]. Under the electron microscope, the virus generally has a roughly spherical shape, from which emerge two glycoproteins (hemagglutinin and neuroaminidase) that are essential to the biology of the virus [3]. Indeed, these enable the virus to adhere to the specific receptors of the cells of the respiratory mucosa and allow the release of the virus that has multiplied inside the cell [4, 5]. Survival of the virus is ensured by the wide variability of its glycoproteins (antigens). Specifically, influenza viruses undergo very frequent point mutations of the genome, which is dispersed in 8 segments of RNA (minor variations). This phenomenon occurs in both A and B viruses, while the genome of A viruses may undergo far more drastic variations (major variations). While minor variations are random, major variations are the result of the hybridization of viruses typical of different animal species (man, swine, birds) [6]. Theoretically, there are 198 possible

combinations of hemagglutinin and neuroaminidase, according to the types of the two known glycoproteins [7]. If, however, minor variations are considered, the number of combinations far exceeds 1 billion. For instance, the virus responsible for the last pandemic, which occurred in 2009/2010, was the result of a quadruple reassortment with two swine virus genes, European and Asian, an avian gene and a human gene [8]. A pandemic usually displays an atypical epidemiological trend (e.g. young adults are particularly affected) [9] and can, according to the pathogenic features of the new virus that causes it, determine even millions of deaths [10, 11].

In the last years of the 20th century and the first years of the 21st, a considerable challenge was posed by the H5N1 virus, which underwent major variations, such as H5N6 and H5N8. Moreover, the possibility currently exists that new subtypes of viruses typical of animals may adapt to humans, as in the case of the H7N9 subtype, which, from March 2013 to April 2015, caused 662 human cases and 262 deaths (lethality: about 40%) [12].

Seasonal influenza generally displays a less severe behavior. Nevertheless, the World Health Organization (WHO) has estimated that the disease causes from 3 to 5 million cases of severe disease and from 250,000 to 500,000 deaths each year, worldwide [13].

Vaccination remains the most efficacious means of mitigating the harmful healthcare and social effects of influenza [14]. Advances in epidemiology, viral genetics, immunology and molecular biology have given a great boost to the preparation of increasingly safe and efficacious vaccines. Thus, influenza vaccines purified by means of chemical methods and containing whole inactivated viruses have given way to split vaccines, subunit vaccines, adjuvated vaccines and live attenuated vaccines [15]. Moreover, the high reliance on supplies of embryonated hen eggs, which are used in traditional vaccine production, has been overcome by the development of vaccines obtained by multiplying the virus in *in vitro* cell cultures [16]. However, notwithstanding the great progress of vaccinology, vaccine efficacy is blunted by the great variability of the pathogen and the need to update vaccine preparations each year in response to the antigen modifications of the virus.

Influenza vaccines have evolved also markedly over time in order to offer broader protection against circulating strains. Indeed, in the early 1960s the vaccine was bivalent, i.e. it contained an H3N2 virus and a B virus; subsequently, trivalent vaccines containing two A viruses and one B virus were developed, and recently, given the co-circulation of both B virus lineages (B/Yamagata and B/Victoria), quadrivalent vaccines were developed.

The recent availability of quadrivalent vaccines constitutes a great advance, in that they can offer broader strain coverage. Indeed, the frequency with which B viruses were isolated by the Italian NIC (National Influenza Center) in the period 2003-2015 ranged from 0.8% to 58.0%, with a mean of 20.5% (95% CI: 0-38%) [17]. Thus, considering that influenza cases in Italy vary on average from 5 to 6 million each year [18], and assuming 38% frequency of B viruses (the upper value of 95% CI) and total B-mismatching, we can suppose that the maximum additional percentage of protection provided by the quadrivalent vaccine may allow us to avoid 2,280.000 cases (at 100% vaccine efficacy; some studies [19, 20] have reported this level of efficacy, albeit rarely) or 1,140.000 cases (50% efficacy). This latter level of efficacy is closer to that reported in most studies. Indeed, a recent meta-analysis conducted by Osterholme revealed mean efficacy levels of 59% in subjects aged between 18 and 65 years, and of 83% in children aged between 6 months and 7 years [21].

Despite the availability of effective and safe influenza vaccines, the Italian public's trust in vaccination has declined. In the last few years, Italian vaccination coverage rates have decreased both among the elderly and among at-risk adults. In the elderly, vaccination coverage declined from 55.6% in the 2013-2014 season to 49.0% in the 2014-2015 season: a fall of 6.6%. However, in comparison with the 2005-2006 season, when coverage was close to 70% (a rate approaching the ideal coverage for subjects aged > 64 years [75%]), the percentage drop was much greater (-21%) [22]. It may plausibly be claimed that one of the reasons for this reduction was poor communication on the part of the Ministry of Health during the pandemic caused by the virus A/California/07/09 [23]; another may have been the excessive prudence of the AIFA, which, for reasons of caution, suspended the use of a commercially available vaccine for two consecutive years [24, 25]. These events were emotively amplified by the press and mass media, and were exploited by anti-vaccination lobbies and consumer associations. As a result, vulnerable subjects were not immunized and were therefore more exposed to the serious complications of the disease. Thus, it is necessary that users, in their own interests, regain trust in this important means of disease prevention. In order to rebuild trust, it must be borne in mind that those who refuse vaccination fall within different categories. Indeed, some oppose vaccination on ideological grounds; some are skeptical of the utility and safety of vaccines; others simply neglect their health, while others again are marginalized individuals. There is also a need to raise awareness among members of the medical profession, since their recommendations are essential to orienting patients towards the right health choices.

Moreover, we cannot ignore the fact that the "anti-vaccinators" hoodwink the gullible with fantastic false accusations that are totally bereft of scientific evidence. Numerous such fallacies have been circulated, such as, for example: "vaccines make women sterile; vaccines shrink the ovaries; vaccines cause testicular cancer; vaccines are contaminated by amoebas present in the air in laboratories; vaccines paralyze the immune system; vaccines cause: Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, transverse myelitis, optical neuritis, diabetes, rheumatoid arthritis, asthma; and so on and so forth. But the greatest of falsehoods spread by the anti-vaccinators is undoubtedly that vaccines cause autism. This lie, which masqueraded as the result of a scientific study, was put about by Dr. Andrew Wake-

field in an article published by the scientific journal The Lancet [26]. It soon emerged, however, not only that Dr. Wakefield had utilized rather unethical para-scientific methods, but also that the results served his own personal interests; he was subsequently struck off the register of British physicians [27]. It is interesting that the anti-vaccinators' claims that vaccines cause neurological or psychiatric disorders are linked in a subtle manner to the "plot hypothesis". Indeed, these people maintain that the plotters (or Illuminated Ones, as they call them) have infiltrated all levels of decision-making in order to foist mass vaccination on the population. The plotters' aims are said to be twofold. First, they want to stultify the majority of the world's people, in order to dominate them more easily, and, at the same time, favor unvaccinated subjects, whose intellectual skills would remain intact as a result of natural selection; second, they want to get rich alongside their industrial allies – the vaccine producers.
The American Institute of Medicine (IOM) has repeatedly demonstrated that there is no scientific evidence to support the much-touted association between vaccines and the above-mentioned diseases [28]. Moreover, in most of the neurological diseases of early onset, the application of molecular biology to neurology is increasingly revealing the importance of transmissible or new-onset genetic disorders, and it has been demonstrated that cases of disease erroneously attributed to vaccination, such as Dravet's syndrome, are actually linked to genetic damage [29].
Vaccination is recognized as one of the most cost-effective in the fight against diseases. However, it is tragic that more than 2½ million children worldwide die each year, despite efficacious and safe vaccines are currently available [30].
In the most advanced countries, such as the USA, vaccination campaigns have always been implemented. However, when a vaccination strategy works well, its results often go unnoticed by the majority of the population. Indeed, only when events occur that threaten public health and arouse mass fears (e.g. measles outbreaks, bioterrorist attacks such as that of the envelopes containing spores of *Bacillus anthracis*, or the threat of biological weapons), does it become clear just how important it is to immunize the population [31]. In Italy, people are now beginning to realize this, in the wake of the various outbreaks of meningococcal invasive disease that have occurred in Tuscany since 2015 [32].
With regard to vaccination policies, it should be pointed out that preventive strategies, despite their great success, have always been an extremely marginal item of expenditure in the Italian National Health Service budget. Indeed, of the total annual expenditure of about € 111 billion, only about € 291 million (0.26%) is spent on vaccination (about € 40 million on influenza vaccines) [33, 34].
In conclusion, in order to mitigate the damage wreaked by influenza, it seems important to strengthen the following interventions:

- improve clinical-epidemiological and virological surveillance of the disease;
- promote the development of new efficacious vaccines, as has recently been done through the introduction of the quadrivalent vaccine;
- extend free vaccination to the entire population, as in the US and Canada [35];
- ensure that general practitioners, pediatricians and other healthcare professionals are properly informed and always updated with regard to vaccination;
- promote public campaigns to raise the population's awareness of the importance of vaccination, not least by using new means of communication such as apps for smartphones and tablets [36, 37];
- inform politicians and other decision-makers of scientific results in the field of vaccination [38];
- fight the anti-vaccination lobbies with such weapons as: counter-information (e.g. what would happen if this or that vaccine had not been invented?), irony, satire, humor, logic, scientific evidence and common sense.

Acknowledgments

No funding declared for this overview.

References

[1] WHO. Influenza (Seasonal). Available at: http://www.who.int/mediacentre/factsheets/fs211/en/ [Accessed on 15/02/16]

[2] Hay A, Gregory V, Douglas A, Lin Y. *The evolution of human influenza viruses*. Philos Trans R Soc Lond B Biol Sci 2001;356:1861-70.

[3] Noda T. *Native morphology of influenza virions*. Front Microbiol 2012;2:269.

[4] Gasparini R, Amicizia D, Lai PL, Bragazzi NL, Panatto D. *Compounds with anti-influenza activity: present and future of strategies for the optimal treatment and management of influenza. Part I: influenza life-cycle and currently available drugs*. J Prev Med Hyg 2014;55:69-85.

[5] Bridges CB, Katz JM, Levandowski RA, Cox NJ. *Inactivated influenza vaccines*. In: Plotkin S, Orenstein W, Offit P (Eds.). *Vaccines*. Fifth Edition. Philadelphia: Saunders Elsevier 2008, pp. 260-90.

[6] Doherty PC, Turner SJ, Webby RG, Thomas PG. *Influenza and the challenge for immunology.* Nature Immunol 2006,7:449-55.

[7] Milligan GN, Barrett ADT. *Vaccinology an essential Guide*. Oxford: Wiley Blackwell 2015.

[8] WHO. Pandemic 2009. Available at: http://www.who.int/csr/disease/swineflu/en/index.html. [Accessed on 16/02/16]

[9] CDC. *Update: novel influenza A (H1N1) virus infection – Mexico, March-May 2009.* MMRW 2009;58:585-9.

[10] Gasparini R, Amicizia D, Lai PL, Panatto D. *Aflunov(®): a prepandemic influenza vaccine.* Expert Rev Vaccines 2012;11:145-57.

[11] Gasparini R, Amicizia D, Lai PL, Panatto D. *Clinical and socioeconomic impact of seasonal and pandemic influenza in adults and the elderly.* Hum Vaccin Immunother 2012;8:21-8.

[12] WHO. *Human cases of influenza at human-animal interface, January 2014-April 2015*. Weekly Epidemiol Record 2015;28:349-64.

[13] WHO. *Influenza*. Available at: http://www.who.int/mediacentre/factsheets/2003/fs211/en/. [Accessed on 16/02/16].

[14] Gasparini R, Pozzi T, Bonanni P, Fragapane E, Montomoli E, Lucioni C. *Valutazione dei costi di un'epidemia influenzale nella popolazione lavorativa di Siena.* Giornale di Farmacoeconomia 2000;4:3-9.

[15] Belshe RB, Walker R, Stoddard JJ, Kemble G, Maassab HF, Mendelman PM. *Influenza vaccine-live*. In: Plotkin S, Orenstein W, Offit P (Eds.). *Vaccines*. Fifth Edition. Philadelphia: Saunders Elsevier 2008, pp. 291-309.

[16] Milián E, Kamen AA. *Current and emerging cell culture manufacturing technologies for influenza vaccines.* Biomed Res Int 2015;2015:504831.

[17] Ministero della Salute. *Sorveglianza virologica dell'influenza*. Available at: http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=771&area=influenza&menu=sorveglianza [Accessed on 15/02/16]

[18] Lai PL, Panatto D, Ansaldi F, Canepa P, Amicizia D, Patria AG, Gasparini R. *Burden of the 1999-2008 seasonal influenza epidemics in Italy: comparison with the H1N1v (A/California/07/09) pandemic*. Hum Vaccin 2011;(Suppl 7):217-25.

[19] Kumpulainen V, Mäkelä M. *Influenza vaccination among healthy employees: a cost-benefit analysis.* Scand J Infect Dis 1997;29:181-5.

[20] Wilde JA, McMillan JA, Serwint J, Butta J, O'Riordan MA, Steinhoff MC. *Effectiveness of influenza vaccine in health care professionals: a randomized trial.* JAMA 1999;281:908-13.

[21] Osterholm MT, Kelley NS, Sommer A, Belongia EA. *Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis.* Lancet Infect Dis 2012;12:36-44.

[22] Rizzo C, Bella A. *Vaccinazione antinfluenzale, i dati di copertura per la stagione 2014-2015.* Epicentro. Available at:: http://www.epicentro.iss.it/problemi/influenza/copertureAntinfluenzale2014-2015.asp. [Accessed on 19/02/16]

[23] Ministero del Lavoro, della Salute e delle Politiche sociali. *L'influenza A è una normale influenza, con queste 5 regole si combatte meglio*. Available at: http://www.salute.gov.it/imgs/C_17_opuscoliPoster_17_allegato.pdf. [Accessed on 19/02/16]

[24] AIFA. *Divieto di utilizzo vaccini influenzali della ditta Novartis Vaccines and Diagnostics*. Available at: http://www.agenziafarmaco.gov.it/it/content/divieto-di-utilizzo-vaccini-influenzali-della-ditta-novartis-vaccines-and-diagnostics. [Accessed on 19/02/16]

[25] AIFA. *AIFA dispone il divieto di utilizzo per due lotti del vaccino antinfluenzale FLUAD*. Available at: http://www.agenziafarmaco.com/it/content/aifa-dispone-il-divieto-di-utilizzo-due-lotti-del-vaccino-antinfluenzale-fluad-0. [Accessed on 19/02/16]

[26] Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. *Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children.* Lancet 1998;351:637-41. Retraction in: Lancet 2010;375:445.

[27] Deer B. *How the case against the MMR vaccine was fixed*. BMJ 2011;342:c5347.

[28] Gasparini R, Panatto D, Lai PL, Amicizia D. *The "urban myth" of the association between neurological disorders and vaccinations.* J Prev Med Hyg 2015;56:E1-8.

[29] Reyes IS, Hsieh DT, Laux LC, Wilfong AA. *Alleged cases of vaccine encephalopathy rediagnosed years later as Dravet syndrome*. Pediatrics 2011;128:e699-e702.

[30] Science technology Society. *Medical interventions*. Available at: https://group2bsn2g.wordpress.com/2007/01/18/medical-interventions/. [Accessed on 19/02/16].

[31] NCSL. *Immunizations policy issues overview*. Available at: http://www.ncsl.org/research/health/immunizations-policy-issues-overview.aspx. [Accessed on 19/02/16].

[32] Epicentro. *Malattie batteriche invasive (sepsi e meningiti).* Available at: http://www.epicentro.iss.it/problemi/meningiti/aggiornamenti.asp. [Accessed on 19/02/16].

[33] ISTAT. *Noi Italia. La spesa sanitaria pubblica assorbe il 7 per cento del Pil*. Available at: http://noi-italia.istat.it/index.php?id=7&user_100ind_pi1%5Bid_pagina%5D=41. [Accessed on 19/02/16].

[34] Osservatorio Nazionale sull'impiego dei medicinali. *L'uso dei farmaci in Italia. Rapporto nazionale 2014.* Available at: http://www.agenziafarmaco.gov.it/sites/default/files/Rapporto_OsMed_2014_0.pdf. [Accessed on 19/02/16].

[35] CDC. *Influenza (Flu)*. Available at: http://www.cdc.gov/flu/. Accesso del 22 febbraio 2016; Public Health Agency of Canada (NACI). Statement on Seasonal Influenza Vaccine for 2015-2016. Documento disponibile al sito web: http://www.phac-aspc.gc.ca/naci-ccni/flu-2015-grippe-eng.php. [Accessed on 22/02/16].

[36] Arnold C. *Flu on the go: mobile technology and respiratory illnesses*. Lancet Respir Med 2015;3:108.

[37] Panatto D, Domnich A, Gasparini R, Bonanni P, Icardi G, Amicizia D, Arata L, Bragazzi NL, Signori A, Landa P, Bechini A, Boccalini S. *Development and preliminary data on the use of a mobile app specifically designed to increase community awareness of invasive pneumococcal disease and its prevention.* Hum Vaccin Immunother 2016;1-5.

[38] Gasparini R, Mennini FS, Panatto D, Bonanni P, Bechini A, Ricciardi W, de Waure C, Marcellusi A, Cicchetti A, Ruggeri M, Boccalini S. *How can the results of Health Technology Assessment (HTA) evaluations applied to vaccinations be communicated to decision-makers and stakeholders? The ISPOR Rome Chapter Project*. J Prev Med Hyg 2015;56:E150-E154.

■ Received on January 15, 2016. Accepted on February 15, 2016.

■ Correspondence: Roberto Gasparini, Department of Health Sciences, via Pastore 1, 16132 Genoa, Italy - Tel. +39 010 3538527 - Fax +39 010 3538541 - E-mail: gasparini@unige.it