HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 3, 712–718
https://doi.org/10.1080/21645515.2017.1420448

Taylor & Francis
Taylor & Francis Group

An infodemiological investigation of the so-called "Fluad effect" during the 2014/2015 influenza vaccination campaign in Italy: Ethical and historical implications

Naim Mahroum[a], Abdulla Watad[a], Roberto Rosselli[b], Francesco Brigo[c], Valentina Chiesa[d], Anna Siri[e], Dana Ben-Ami Shor[f], Mariano Martini[e,g,*], Nicola Luigi Bragazzi [e,g], and Mohammad Adawi[h,*]

[a]Department of Medicine 'B', Sheba Medical Center, Tel-Hashomer, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [b]Local Health Unit 3 of Genoa (ASL3 Genovese), Hygiene and Public Health Unit, Genoa, Italy; [c]Department of Neuroscience, Biomedicine and Movement Science, University of Verona, Verona and Division of Neurology, "Franz Tappeiner" Hospital, Merano, Italy; [d]Department of Biomedical, Biotechnological and Translational Sciences, University of Parma, Parma, Italy; [e]UNESCO CHAIR "Anthropology of Health – Biosphere and Healing System", University of Genoa, Genoa and Department of Mathematics (DIMA), University of Genoa, Genoa, Italy; [f]Department of Gastroenterology, Sheba Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [g]Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy; [h]Padeh and Ziv hospitals, Bar-Ilan University, Faculty of Medicine, Zefat, Israel

ABSTRACT

Influenza vaccines represent a major tool to contain the clinical and epidemiological burden generated by influenza. However, in spite of their effectiveness, vaccines are victims of prejudices and false myths, which contribute to the increasing phenomenon of vaccine hesitancy and loss of confidence. Media and, mainly, new media, and information and communication technologies play a major role in disseminating health-related information. While, on the one hand, they can be extremely promising in promoting disease prevention, on the other hand, they can also have a negative impact on population's health attitudes and behaviors when delivering information not based on scientific evidences. The "Fluad-case" is an excellent example of the crucial role of an adequate information campaign. Following the cluster of deaths allegedly related to the administration of the adjuvanted influenza vaccine "Fluad" during the 2014–2015 influenza campaign, the Italian health authorities and regulatory bodies decided the withdrawal of two potentially contaminated Fluad batches. This fostered a huge media coverage, with resulted in negatively impacting on influenza vaccination coverage. Monitoring and tracking the Fluad-related web searches, we showed that Liguria resulted the Italian region with the highest number of Fluad-related website searches and that, interestingly, Fluad was searched also in Regions in which this vaccine was not distributed. A positive moderate correlation between accessing Fluad-related websites and overall influenza vaccination coverage was found ($r = 0.66$ ([95%CI 0.29–0.86], $p = 0.0026$). Considering subjects $\geq$65 years, who are the subjects for which the Fluad vaccination is recommended, the correlation resulted $r = 0.49$ ([95%CI 0.03–0.78], $p = 0.0397$). As such, health authorities and decision-makers should promote high-quality communication campaigns in order to raise awareness of vaccination practices.

ARTICLE HISTORY
Received 10 November 2017
Accepted 19 December 2017

KEYWORDS
ethics of health communication and vaccination; Fluad; influenza vaccine and influenza vaccination campaign; infodemiology; web 2.0

Introduction

Influenza, a highly contagious acute viral disease, is one of the most common human respiratory infections, and can impose a high burden in terms of morbidity and mortality, mainly among the elderly and subjects with co-morbidities, as well as in terms of costs.[1-4] Vaccines are one of most effective preventive tools that can be used in order to contain influenza outbreaks and to reduce or, at least, mitigate its economic and societal burden. However, controversies and concerns about vaccine safety and effectiveness as well as a low risk perception of getting influenza have lead to a significant decrease in the immunization rates.[1-3]

The consequences of vaccine hesitancy and refusal are of great concern. For instance, Phadke *et al.*[5]have concluded, in their review article on recent preventable diseases outbreaks in the USA, that a substantial proportion of measles cases were intentionally unvaccinated. The phenomenon of vaccine refusal was associated with an increased risk for measles among people who refused vaccines as well as among fully vaccinated individuals. Refusal of pertussis vaccine was associated with an increased risk for pertussis in some populations, as also shown by Feikin *et al.*[6]Glanz and coworkers.[7]documented high risk in children of parents who refused pertussis immunization. These findings stress the need to better understand why some parents and, more generally speaking, some subjects refuse immunization practices in order to develop strategies for conveying the risks and benefits of immunizations to parents more effectively.[8]

Nowadays, in the era of the dynamic Web 2.0 and within the framework of the so-called e-health, the new information and

CONTACT Nicola Luigi Bragazzi, MD, PhD, MPH robertobragazzi@gmail.com Postgraduate School of Public Health, Department of Health Sciences (DISSAL), University of Genoa, Via Antonio Pastore 1, Genoa, 16132, Italy.

*These authors contributed equally to this work.

communication technologies (ICTs), such as social networks, are widely available and play a pivotal role in the distribution and dissemination of health-related information including vaccination practices.[9]Both the quantity and quality of influenza vaccination related information may negatively/positively affect immunization programs.[10,11]

During the influenza season of 2014–2015, in Italy, in the week from 12th to 18th November 2014, three deaths occurred shortly after the administration of Fluad, an inactivated trivalent influenza vaccine, adjuvanted with an oil-in-water emulsion adjuvant (squalene, sodium citrate dihydrate, citric acid monohydrate, polysorbate 80, sorbitan trioleate, MF59C.1), manufactured in Italy by Novartis (Novartis Vaccines and Diagnostics, Inc., NVD), first approved for use in Europe in 1997 and authorized in a number of European Union countries, including Austria, Belgium, Germany, Denmark, Greece, Spain, France, Ireland, Luxembourg, Portugal, and Sweden, as well as in Italy. The first case occurred in a 68-year-old subject who died of myocardial infarction several hours following vaccination. The two other cases occurred in 79- and 87-year-old subjects who died of meningo-encephalitis approximately 48 hours following vaccination. Other deaths followed and were reported through the National Network of Pharmacovigilance (NNP). The Italian Medicines Agency (AIFA) decided to suspend the use of Fluad vaccine immediately following these cases. Both the AIFA and the Italian Institute of Health (ISS) carried out investigations concerning this cluster of deaths, in agreement with the European Medicines Agency (EMA). Even though the Pharmacovigilance Risk Assessment Committee (PRAC), EMA, ISS and AIFA concluded that there was no evidence that Fluad vaccine administration caused deaths in Italy. Based on the World Health Organization (WHO) causality assessment, 45 of the overall 66 deaths occurred during the 2014–2015 influenza vaccination campaign were unrelated to the vaccination administration. However, media hypes surrounding the so-called "Fluad case" have negatively affected the 2014–2015 influenza immunization campaign.[12]

In 2002, Gunther Eysenbach has coined the term "infodemiology" (a *port-manteau* of information and epidemiology) to indicate the new emerging "science of distribution and determinants of information in an electronic medium, specifically the Internet, or in a population, with the ultimate aim to inform and improve public health and public policy".[13,14]

Eysenbach demonstrated a correlation between flu-related web searches and real-world epidemiological data, namely flu-incidence data.[15]As such, systematically collecting and analyzing health-related demand-based data from the Internet could be exploited for syndromic surveillance as well as for capturing the public reaction to an outbreak. Tracking web searches has, indeed, the potential to predict population-based events relevant for public health purposes, such as outbreaks, but may also be affected by distortions, misinformation and biases – the so-called "epidemics of fear". Health authorities could exploit ICTs for real-time content analysis of the online posted material, promptly responding to public concerns and prejudices.[16]

In the current study, in which we applied an infodemiological approach and we tracked and monitored web searches, we aimed to assess the impact of the "Fluad case" on the public awareness in terms of web-related activities. Web-searches in all Italian regions have been analyzed in that the National Health System (NHS) has a segmented, composite nature, being mainly under the control of regional governments, and is administered by and articulated in local health authorities or local health unities (LHAs/LHUs). Health policy relies on the principles of decentralisation and federalism, even though the so-called essential levels of healthcare (ELHs) are guaranteed throughout the Italian territory. Influenza vaccination coverage significantly varies among the Regions: for instance, during the 2014–2015 campaign, the overall coverage rate was 49.0%, with the minimum decrease (3.3%) in Lombardy and the maximum decrease (28.0%) in Abruzzo with respect to the previous influenza vaccination campaign.

Results

A detailed timeline of the so-called "Fluad case" is shown in Table 1, to which the reader is kindly referred. During the entire influenza vaccination campaign, 66 deaths occurred (35 after the administration of Fluad). Concerning specifically Fluad, AIFA received 130 safety concerns (rate 4 per 100,000 Fluad doses), with 62.3% of them being severe or extremely severe.

Concerning the infodemiological analysis, the patchy nature of the digital interest is represented in Fig. 1. More in details, Liguria resulted the Italian region with the highest number of Fluad-related website searches (Table 2). Interestingly, Fluad was searched also in Regions in which this vaccine was not distributed (Table 2). Furthermore, the Google Trends (GT)-generated curves at each regional level cannot be perfectly superposed with the GT-generated curve at national level: different temporal peaks can, indeed, be noticed (Table 3). GT-curves seem to differ from Region to Region both in terms of search volumes and temporal peaks (Table 2 and Table 3), suggesting that the "Fluad effect" may have had peculiar local characteristics. This could be due also to the different socio-demographic characteristics of Italian regions, in terms of economic, digital-behavioral and socio-cultural features (Table 2). For example, it could be noticed that search volumes in Regions with low Gross Domestic Product (GDP) values (such as Sicily or Campania) were low even though Fluad was employed in these Regions.

Political/juridical initiatives (such as enquiries opened by judges or decision to suspend the influenza vaccination campaign) could have also had an impact on search volumes.

Furthermore, there seems to be a positive moderate correlation between accessing Fluad-related websites and overall influenza vaccination coverage, yielding a coefficient $r = 0.66$ ([95%CI 0.29–0.86], $p = 0.0026$) (Fig. 2). Considering subjects ≥65 years, who are specifically the subjects for which the Fluad vaccination is recommended, the correlation resulted low, with $r = 0.49$ ([95%CI 0.03–0.78], $p = 0.0397$) (Fig. 3).

Interestingly, Liguria Region is in two different locations in Fig. 2 and 3: while there is a high correspondence between search volume and decrease in overall influenza vaccination coverage rate (Fig. 2), this does not hold or holds with less strength when examining coverage rate among subjects ≥65 years (Fig. 3), probably indicating an age-dependent effect.

Table 1. Timeline of the Fluad-case. Abbreviations: AIFA (Italian Medicines Agency); EMA (European Medicines Agency); FIMMG (Italian Federation of General Practitioners); ISS (Italian Institute of Health); LHU (Local Health Unit); NNP (National Network of Pharmacovigilance); PRAC (Pharmacovigilance Risk Assessment Committee); WHO (World Health Organization).

DAY	EVENT
7th-18th November 2014	A first cluster of 3 deaths allegedly associated with the Fluad vaccine administration occurred on 7th, 12th and 16th November was reported through the NNP (2 deaths in Sicily – a man of 68 years and a woman of 87 years – and 1 death in Molise – a woman of 79 years)
15th-28th November 2014	A second cluster of 8 deaths possibly linked to the Fluad vaccine administration was reported through the NNP
26th November 2014	Death of a 83-year old woman in Spoleto (Umbria), with several co-morbidities, 24 hours after the immunization
27th November 2014	AIFA decided to suspend two Fluad batches (ID 142701 and ID 143301) on the basis of the precautionary principle AIFA issued two press releases (number 401 and number 402), commenting on the decision of recalling two Fluad batches and emphasizing that the withdrawal was on a precautionary basis and vaccines represent an effective tool, being "a unique and irreplaceable resource"
28th November 2014	AIFA issued three press releases (n. 403, n. 404, and n. 405), commenting on 11 deaths allegedly associated to Fluad vaccination and emphasizing the urgent need of going on with the influenza vaccination campaign. Lazio Region decided to suspend and recall all Fluad batches (protocol number 664796/GR/11/02, entitled "Precautionary recall of anti-influenza Fluad vaccine"). Liguria Region decided to suspend temporarily the entire anti-influenza vaccination campaign
29th November 2014	AIFA issued two press releases (n. 406 and n. 407), listing 12 deaths potentially linked to Fluad administration reported through NNP
30th November 2014	A 83-year old woman with several co-morbidities died apparently some hours after receiving the anti-influenza immunization NNP listed 13 deaths as potentially related to the Fluad vaccine administration, distributed among 8 different Regions AIFA issued a press release (n. 407), commenting on the 13 deaths reported through NNP
1st December 2014	ISS released the first safety results, which showed no anomalies AIFA issued a press release (n. 409), reporting 19 safety concerns regarding 8 Fluad batches and commenting on ISS preliminary safety results Italian television and newspaper journalist Bruno Vespa, Professor Dr. Luca Pani, Director General of AIFA, Prof. Dr. Walter Ricciardi of the ISS, and Dr. Giacomo Milillo Secretary General of the FIMMG were publicly vaccinated in TV, to reinsure public opinion about Fluad safety
2nd December 2014	20 deaths allegedly associated to Fluad administration reported through NNP and related to 8 Fluad batches
3rd December 2014	EMA released the PRAC conclusion ("PRAC advice"): on the basis of the WHO causality assessment, 45 deaths resulted uncorrelated with the vaccine administration (the remaining 21 deaths were considered as unclassifiable, because of the dearth of clinical information) AIFA issued a press release (n. 410), commenting on the PRAC conclusion Professor Dr. Sergio Pecorelli, President of AIFA, stated that it is of extreme importance to work for rebuilding a sense of confidence and trust towards vaccines
19th December 2014	Questions tabled in Parliament (question Dellai and Binetti n. 2–00770; question Silvia Giordano and Cecconi n. 2–00772)
23rd December 2014	ISS released the final safety results AIFA issued a press release (n. 413), communicating the final safety results carried out by ISS and stopping the recall and withdrawal of Fluad batches ID 142701 and ID 143301

At a multivariate regression analysis, socio-demographic variables did not result to have a significant effect on Fluad-related RSV (population size $p = 0.200$; GDP per capita $p = 0.751$; educational level $p = 0.948$; Internet penetration index $p = 0.447$). Regions in which the recalled Fluad batches had been redistributed has a higher statistically significant RSV (64.09 ± 6.29 [95%CI 50.75–77.43] *versus* 42.00 ± 7.89 [95%CI 25.28–58.72], $p = 0.044$). Regions in which alleged Fluad-related deaths occurred had higher RSV (62.55 ± 6.60 [95%CI 48.57–76.53] *versus* 44.43 ± 8.27 [95%CI 26.90–61.95]) even though this was not statistically significant ($p = 0.106$). Finally, Regions in which influenza vaccination campaign was suspended (even if temporarily) reported higher RSV (73.00 ± 16.17 [95%CI 38.72–100.00] *versus* 53.31 ± 5.72 [95%CI

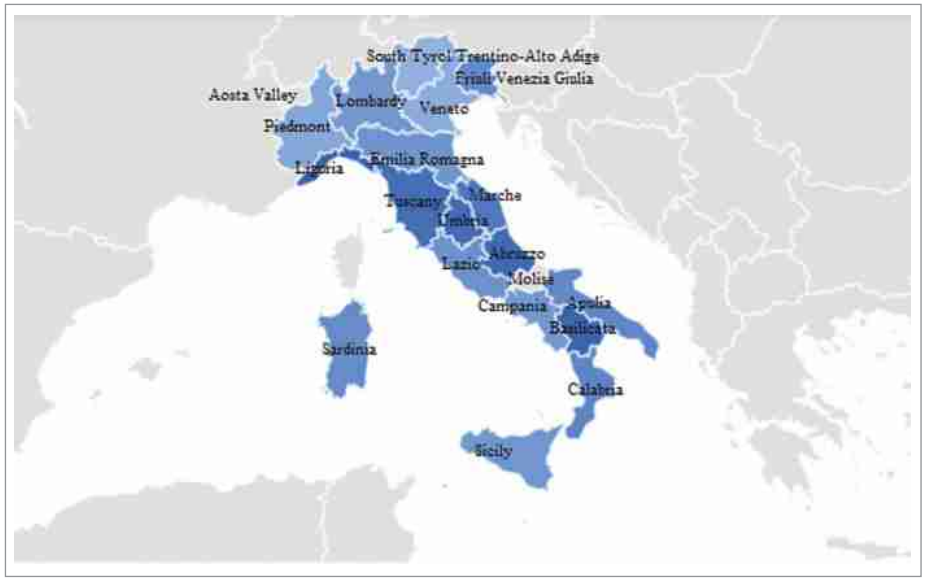

Figure 1. Heat-map showing the digital interest for Fluad-related online material, as captured by Google Trends, searched during the 2014/2015 influenza vaccination campaign, showing the patchy nature of the Fluad-related online behavior.

Table 2. Ranking of Italian regions according to the volumes of Fluad-related web-searches during the study period, as captured by Google Trends (GT). Socio-demographic information and details have been taken from the Italian National Statistical Institute (ISTAT) and from the European Statistical Institute (EUROSTAT). GT data for Aosta Valley and Molise are not available, due to insufficient search volumes. Abbreviations: GDP (gross domestic product); RSV (relative search volume).

Region	Population size	GDP per capita (in k€)	Educational evel (participation of adults aged 25–64 in education and training)	Internet penetration index (%)	RSV (%)	Distribution of the two Fluad recalled batches (ID 142701 and ID 143301)	Alleged Fluad-related deaths	Sospension of Fluad
Liguria	1,591,939	29.0	7.1	55	100	✓	✓	✓
Basilicata	578,391	18.7	6.4	49	92	✓	✓	
Abruzzo	1,333,939	23.1	7.5	52	83	✓	✓	
Umbria	896,742	23.9	7.9	53	81		✓	
Tuscany	3,750,511	28.9	7.8	58	80	✓	✓	
Marche	1,553,138	25.2	7.4	57	64	✓		
Calabria	1,980,533	16.2	5.4	44	55	✓		
Apulia	4,090,266	16.9	5.0	49	53	✓	✓	
Friuli-Venezia Giulia	1,229,363	27.9	7.5	60	52			
Sardinia	1,663,859	19.8	7.6	57	50	✓		
Lazio	5,870,451	31.7	7.4	57	46	✓	✓	✓
Emilia-Romagna	4,446,354	32.5	7.4	59	44		✓	
Sicily	5,094,937	17.0	4.8	47	42	✓	✓	
Lombardy	9,973,397	35.0	6.6	59	41		✓	
Campania	5,869,965	16.8	5.7	44	40	✓		
Piedmont	4,436,798	27.8	6.5	55	29			
Veneto	4,926,818	30.0	6.2	60	26		✓	
Trentino-Alto Adige	1,051,951	36.9	9.7	62	21			

41.19–65.43]) even though this was not statistically significant ($p = 0.268$).

Discussion

Given the segmented nature of the Italian NHS and its implementation of the health policy, we decided to monitor and track the Fluad-related web searches both at a national and a regional level. Exploiting GT, we showed that Liguria resulted the Italian region with the highest number of Fluad-related website searches. We could speculate that this digital behavior could reflect the unprecedented and unique decision of Liguria Region to suspend the entire influenza vaccination campaign (even though this decision was heavily criticized and, subsequently, the Region decided to resume the vaccination campaign). Furthermore, interestingly, Fluad was searched also in Regions in which the recalled Fluad vaccine batches had not been distributed. Intriguingly, a statistically significant correlation between accessing Fluad-related websites and influenza vaccination coverage was found.

Using an infodemiological approach, our study has addressed the impact of media and, especially, of ICTs, in communicating health-related information on vaccination coverage.[17,18]

According to the National Communication Association, communication "focuses on how people use messages to generate meanings within and across various contexts, and is the discipline that studies all forms, modes, media, and consequences of communication through humanistic, social scientific, and aesthetic inquiry".[19]

Health communication specifically deals with health-related issues including their societal resonance and impact, thus playing a major role in epidemiology and preventive medicine. For example, Beato and Telfer.[20]defined communication as an essential component of health science and illustrated diverse

Table 3. Main characteristics and peaks of the different Google Trends (GT)-generated curves at regional level, during the time period, as captured by GT. Google-Trends data for Aosta Valley and Molise are not available, due to insufficient search volumes.

Region	27th November 2014 peak	1st December 2014 peak	3rd December 2014 peak	23rd December 2014 peak
Liguria	✓		✓	
Basilicata	✓			
Abruzzo	✓			
Umbria	✓			
Tuscany	✓			
Marche	✓			✓
Calabria	✓			
Apulia	✓			
Friuli-Venezia Giulia	✓			
Sardinia	✓			
Lazio	✓	✓		✓
Emilia-Romagna	✓	✓	✓	✓
Sicily	✓	✓	✓	
Lombardy	✓			✓
Campania	✓		✓	✓
Piedmont	✓	✓		
Veneto	✓	✓		
Trentino-Alto Adige				
Italy (overall)	✓	✓	✓	✓

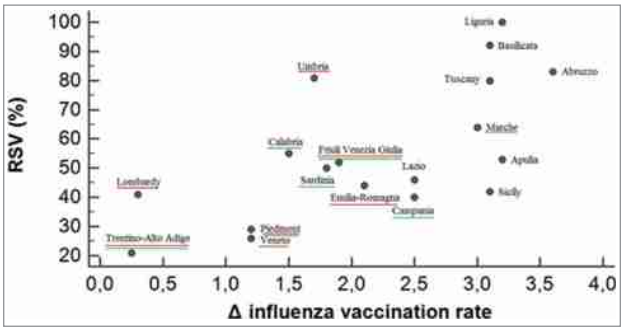

Figure 2. Correlation between digital interest for Fluad-related online material and decrease in influenza vaccination coverage rate between 2013/2014 and 2014/2015 vaccination campaigns (data per 100 inhabitants). Google-Trends data for Aosta Valley and Molise are not available, due to insufficient search volumes. Underlined in red the Regions in which the recalled Fluad vaccine batches had not been distributed; underlined in green the Regions in which no alleged Fluad-related deaths occurred.

examples in which health communication was found to be able to protect public health against disastrous and dangerous events such as Hurricane Katrina, H1N1 influenza pandemics, and concerns about chemical exposure in imported drywall, among others. Further, the US Department of Health and Human Services (HHS) has maintained that during the first decade of the 21st century, health communication has played a major role in improving both personal and community health.[21]

Monitoring and tracking web-searches related to important public health issues such as vaccination as carried out in the recent paper by Bragazzi *et al.*[18]has shown that most users seek information about possible vaccine-related side-effects. As such, ICTs can have a positive influence on parental vaccine-related knowledge, attitudes, beliefs and vaccination willingness, but can also lead to misinformation and vaccine concerns and problematization.

Specifically focusing on the so-called "Fluad case", it received a wide media coverage in Italy during the influenza season of 2014–2015, after the deaths of three people allegedly related to the administration of Fluad vaccine. Odone *et al.*[22]quantitatively analyzed the Fluad-related media coverage and showed that most of reports/news concerning the "Fluad case" were released and published during the so-called "uncertainty period", that is

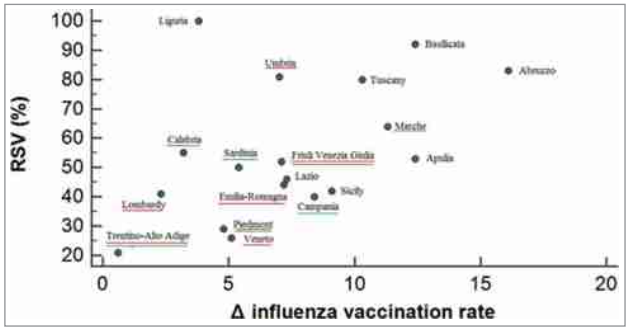

Figure 3. Correlation between digital interest for Fluad-related online material and decrease in influenza vaccination coverage rate between 2013/2014 and 2014/2015 vaccination campaigns in subjects aged ≥65 years (data per 100 inhabitants). Google-Trends data for Aosta Valley and Molise are not available, due to insufficient search volumes. Underlined in red the Regions in which the recalled Fluad vaccine batches had not been distributed; underlined in green the Regions in which no alleged Fluad-related deaths occurred.

to say the time period between the three deaths and the final announcements of both the Italian and European regulatory agencies which disproved any causal relationship between the Fluad administration and the deaths. On the contrary, these announcements attracted scarce media coverage.

As stated by Levi and colleagues.[23]and demonstrated by Capanna *et al.*[24]and by Rosselli and coworkers,[25] this biased, unbalanced media coverage has contributed to further reducing vaccine confidence in the general population and to decreasing vaccination coverage, emphasizing once again the importance of a proper communication on vaccine safety issues. Given the role of health communication, a collaboration between health workers and public health communication practitioners should be considered fundamental in order to prevent the dissemination of information not based on scientific evidence and to maintain and ensure an adequate immunization coverage.

Our study based on the Fluad-related web-searches has quantitatively characterized the impact of the so-called "Fluad case", both at a national and regional level, showing a correlation between the amount of web-searches and the decrease in influenza vaccination coverage rate between 2013/2014 and 2014/2015 vaccination campaigns. This approach of investigating the web searches taking into account the segmented, composite nature of the Italian NHS undoubtedly represents the major strength of our research.

However, our study has a number of shortcomings that should be adequately acknowledged. First of all, GT does not provide scholars with raw, absolute data, hindering, as such, further mathematical/statistical processing and manipulation. Moreover, GT only captures a particular segment of the population: namely, that fraction, which uses the new ICTs and, in particular, Google as search engine (even though Google is the most common and popular search engine worldwide). On the other hand, the number of subjects utilizing the new media is increasingly growing, narrowing the so-called "digital divide" or "digital gap".

Conclusion

Influenza vaccination coverage is still suboptimal despite the scientific and institutional recommendations and the proven effectiveness of influenza immunization in mitigating influenza-related co-morbidities and deaths. Our study, showing the negative impact of the so-called "Fluad case" on vaccine uptake from a quantitative standpoint, underlines the crucial role of health communication in delivering correct information, not based on myths and prejudices but on facts and scientific evidences. As such health authorities and decision-makers should promote high-quality communication campaigns in order to raise awareness of vaccination practices. Furthermore, being conducted both at a national and regional levels, this study has practical implications for national/regional decision- and policy-makers, as well as for healthcare professionals.

Material and methods

Timeline of the so-called "Fluad case"

In order to temporally reconstruct the so-called "Fluad case", the following websites were systematically consulted: the site of

AIFA (http://www.agenziafarmaco.gov.it/), the site of ISS (http://www.iss.it/), the site of EpiCentro (http://www.epicentro.iss.it/), the site of the Ministry of Health (http://www.salute.gov.it/portale/home.html), and the site of EMA (http://www.ema.europa.eu/ema/).

Big data analysis

A Big Data analysis was carried out, using GT (openly accessible at https://www.google.it/trends), a tool that enables to track and monitor web searches performed surfing Google as search engine. GT has been mined during the 2014/2015 influenza campaign, searching for Fluad-related content written in Italian language, using "Fluad" as key-word and exploiting an *in-house* script, which facilitated data collection and parsing, as previously described in details.[26-34] It is important to stress that GT-generated data are relative and not absolute, and raw volume data are not provided. Further, they are provided already normalized according to the geographic area and to the time window chosen.

Socio-demographic data

In order to provide more insights on the infodemiological analysis, socio-demographic data (population size, GDP per capita and Internet penetration index) were taken from the Italian "National Statistical Institute" (ISTAT, available at https://www.istat.it/en/) and from the European Statistical Institute (EUROSTAT, available at http://ec.europa.eu/eurostat/statistics-explained/index.php/Educational_attainment_statistics).

Statistical analysis

Pearson correlation was carried out between digital interest and real epidemiologic data concerning influenza vaccination coverage rates. The strength of correlation was measured using the following rule of thumb: negligible correlation with r coefficient in the range 0.00–0.30, low correlation with r in the range 0.30–0.50, moderate correlation with r in the range 0.50–0.70, high correlation with r in the range 0.70–0.90, and very high correlation with r in the range 0.90–1.00.

Concerning influenza vaccination coverage rates, decrease was computed between influenza vaccination coverage rate during the 2013/2014 and 2014/2015 vaccination campaigns (data per 100 inhabitants).

Multivariate regression analyses were carried out in order to dissect potential determinants of Fluad-related digital behavior.

Statistical analyses were carried out using the commercial software "Statistical Package for Social Sciences" (SPSS) for Windows (version 23.0.0, Chicago, IL, USA) and MedCalc Statistical Software v16.4.3 (MedCalc Software bvba, Ostend, Belgium).

Figures with p-value <0.05 were considered statistically significant.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors acknowledge the anonymous referees who helped to improve the quality of the manuscript. The authors also thank the other components of the "Fluad Effect Working Group": Valter Turello, Anna Opisso, Laura Arenare, Franco Amadio Petrucci.

ORCID

Nicola Luigi Bragazzi http://orcid.org/0000-0001-8409-868X

References

1. 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 Sep;55(3):69–85.
2. 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 II: Future compounds against influenza virus. J Prev Med Hyg. 2014 Dec;55(4):109–29.
3. Barberis I, Myles P, Ault SK, Bragazzi NL, Martini M. History and evolution of influenza control through vaccination: From the first monovalent vaccine to universal vaccines. J Prev Med Hyg. 2016 Sep;57(3):E115–E120.
4. Peteranderl C, Herold S, Schmoldt C. Human Influenza Virus Infections. Semin Respir Crit Care Med. 2016;37(4):487–500. doi:10.1055/s-0036-1584801. PMID:27486731.
5. Phadke VK, Bednarczyk RA, Salmon DA, Omer SB. Association Between Vaccine Refusal and Vaccine-Preventable Diseases in the United States: A Review of Measles and Pertussis. JAMA. 2016 Mar 15;315(11):1149–58. doi:10.1001/jama.2016.1353.
6. Feikin DR, Lezotte DC, Hamman RF, Salmon DA, Chen RT, Hoffman RE. Individual and community risks of measles and pertussis associated with personal exemptions to immunization. JAMA. 2000 Dec 27;284(24):3145–50. doi:10.1001/jama.284.24.3145.
7. Glanz JM, McClure DL, Magid DJ, Daley MF, France EK, Salmon DA, Hambidge SJ. Parental refusal of pertussis vaccination is associated with an increased risk of pertussis infection in children. Pediatrics. 2009 Jun;123(6):1446–51. doi:10.1542/peds.2008-2150.
8. Salmon DA, Dudley MZ, Glanz JM, Omer SB. Vaccine hesitancy: Causes, consequences, and a call to action. Vaccine. 2015 Nov 27;33 Suppl 4:D66–71. doi:10.1016/j.vaccine.2015.09.035.
9. Bragazzi NL. From P0 to P6 medicine, a model of highly participatory, narrative, interactive, and "augmented" medicine: Some considerations on Salvatore Iaconesi's clinical story. Patient Prefer Adherence. 2013 Apr 24;7:353–9. doi:10.2147/PPA.S38578.
10. Nawa N, Kogaki S, Takahashi K, Ishida H, Baden H, Katsuragi S, Narita J, Tanaka-Taya K, Ozono K. Analysis of public concerns about influenza vaccinations by mining a massive online question dataset in Japan. Vaccine. 2016 Jun 8;34(27):3207–13. doi:10.1016/j.vaccine.2016.01.008.
11. Amicizia D, Domnich A, Gasparini R, Bragazzi NL, Lai PL, Panatto D. An overview of current and potential use of information and communication technologies for immunization promotion among adolescents. Hum Vaccin Immunother. 2013 Dec;9(12):2634–42. doi:10.4161/hv.26010.
12. Signorelli C, Odone A, Conversano M, Bonanni P. Deaths after Fluad flu vaccine and the epidemic of panic in Italy. BMJ. 2015 Jan 14;350:h116. doi:10.1136/bmj.h116.
13. Eysenbach G. Infodemiology and infoveillance: Framework for an emerging set of public health informatics methods to analyze search, communication and publication behavior on the Internet. J Med Internet Res. 2009 Mar 27;11(1):e11. doi:10.2196/jmir.1157.
14. Eysenbach G. Infodemiology: Tracking flu-related searches on the web for syndromic surveillance. AMIA Annu Symp Proc. 2006:244–8. PMID:17238340.

15. Chew C, Eysenbach G. Pandemics in the age of Twitter: Content analysis of Tweets during the 2009 H1N1 outbreak. PLoS One. 2010 Nov 29;5(11):e14118. doi:10.1371/journal.pone.0014118.
16. Eysenbach G. Infodemiology: The epidemiology of (mis)information. Am J Med. 2002 Dec 15;113(9):763–5. doi:10.1016/S0002-9343(02)01473-0.
17. Rosselli R, Martini M, Bragazzi NL. The old and the new: Vaccine hesitancy in the era of the Web 2.0. Challenges and opportunities. J Prev Med Hyg. 2016;57(1):E47–50. PMID:27346940.
18. Bragazzi NL, Barberis I, Rosselli R, Gianfredi V, Nucci D, Moretti M, Salvatori T, Martucci G, Martini M. How often people google for vaccination: Qualitative and quantitative insights from a systematic search of the web-based activities using Google Trends. Hum Vaccin Immunother. 2017 Feb;13(2):464–469. doi:10.1080/21645515.2017.1264742.
19. National Communication Association: https://www.natcom.org/.
20. Beato RR, Telfer J. Communication as an essential component of environmental health science. J Environ Health. 2010;73(1):24–5. PMID:20687329
21. U.S. Department of Health and Human Services. Healthy People 2010: Understanding and Improving Health. 2nd ed. Washington, DC: U.S. Government Printing Office, November 2000.
22. Odone A, Chiesa V, Ciorba V, Cella P, Pasquarella C, Signorelli C. Influenza and immunization: A quantitative study of media coverage in the season of the «Fluad case». Epidemiol Prev. 2015;39(4 Suppl 1):139–45. PMID:26499432.
23. Levi M, Sinisgalli E, Lorini C, Santomauro F, Chellini M, Bonanni P. The "Fluad Case" in Italy: Could it have been dealt differently? Hum Vaccin Immunother. 2017 Feb;13(2):379–384. doi:10.1080/21645515.2017.1264738.
24. Capanna A, Gervasi G, Ciabattini M, Volpe E, Spadea A, Sgricia S, Zaratti L, Franco E. Effect of mass media on influenza vaccine coverage in the season 2014/2015: A regional survey in Lazio, Italy. J Prev Med Hyg. 2015 Aug 5;56(2):E72–6.
25. Rosselli R, Martini M. The Fluad Effect Working Group, Bragazzi NL, Watad A The Public Health Impact of the So-Called "Fluad Effect" on the 2014/2015 Influenza Vaccination Campaign in Italy: Ethical Implications for HealthCare Workers and Health Communication Practitioners. Adv Exp Med Biol. 2017, in press. doi:10.1007/5584_2017_39. PMID:28452003.
26. Alicino C, Bragazzi NL, Faccio V, Amicizia D, Panatto D, Gasparini R, Icardi G, Orsi A. Assessing Ebola-related web search behaviour: insights and implications from an analytical study of Google Trends-based query volumes. Infect Dis Poverty. 2015 Dec 10;4:54. doi:10.1186/s40249-015-0090-9.
27. Bragazzi NL, Dini G, Toletone A, Brigo F, Durando P. Infodemiological data concerning silicosis in the USA in the period 2004–2010 correlating with real-world statistical data. Data Brief. 2016 Nov 13;10:457–464. doi:10.1016/j.dib.2016.11.021.
28. Bragazzi NL, Bacigaluppi S, Robba C, Siri A, Canepa G, Brigo F. Infodemiological data of West-Nile virus disease in Italy in the study period 2004–2015. Data Brief. 2016 Nov 2;9:839–845. doi:10.1016/j.dib.2016.10.022.
29. Bragazzi NL, Dini G, Toletone A, Brigo F, Durando P. Leveraging Big Data for Exploring Occupational Diseases-Related Interest at the Level of Scientific Community, Media Coverage and Novel Data Streams: The Example of Silicosis as a Pilot Study. PLoS One. 2016 Nov 2;11(11):e0166051. doi:10.1371/journal.pone.0166051.
30. Bragazzi NL, Amital H, Adawi M, Brigo F, Watad S, Aljadeff G, Amital D, Watad A. What do people search online concerning the "elusive" fibromyalgia? Insights from a qualitative and quantitative analysis of Google Trends. Clin Rheumatol. 2017, in press. doi:10.1007/s10067-017-3665-y.
31. Siri A, Khabbache H, Al-Jafar A, Martini M, Brigo F, Bragazzi NL. Infodemiological data of high-school drop-out related web searches in Canada correlating with real-world statistical data in the period 2004–2012. Data Brief. 2016 Oct 13;9:679–684. doi:10.1016/j.dib.2016.09.032.
32. Mnadla S, Bragazzi NL, Rouissi M, Chaalali A, Siri A, Padulo J, Ardigò LP, Brigo F, Chamari K, Knechtle B. Infodemiological data of Ironman Triathlon in the study period 2004–2013. Data Brief. 2016 Aug 27;9:123–7. doi:10.1016/j.dib.2016.08.040.
33. Bragazzi NL, Bacigaluppi S, Robba C, Nardone R, Trinka E, Brigo F. Infodemiology of status epilepticus: A systematic validation of the Google Trends-based search queries. Epilepsy Behav. 2016 Feb;55:120–3. doi:10.1016/j.yebeh.2015.12.017.
34. Bragazzi NL, Martini M, Igwe SC, Vecchio I, Borromeo F, Barberis I, Licata M, Brigo F, Cardinale AE, Adawi M. Has the ice bucket challenge really increate people's awareness of amyotrophic lateral sclerosis? Insights and ethical implications from Google Trends and Wikipedia: A 2 years-follow up. Acta Medica Mediterranea. 2017, in press.