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Deliverable 1.7

Analysis of key issues and gaps about perception and knowledge on benefits and risks of vaccines

WP1 – Best practice and code of conduct for benefit-risk monitoring of vaccines

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ADVANCE vision is focused to deliver "best evidence at the right time to support decision-making on vaccination in Europe". Our mission is to prototype a sustainable and compelling system that rapidly provides best available scientific evidence on vaccination benefits and risks post-licensure for well informed decisions. This will be achieved by developing and testing a code of conduct, rules of governance, technical infrastructures, data sources, methods, and workflows in a European network of stakeholders.

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DEFINITIONS

Participants of the ADVANCE Consortium are referred to herein according to the following codes:

- **AUH.** Aarhus Universitetshospital (Denmark)
- **AEMPS.** Agencia Española de Medicamentos y Productos Sanitarios (Spain)
- **ASLCR.** Azienda Sanitaria Locale della Provincia di Cremona (Italy)
- **CRX**. Crucell Holland BV (Netherlands)
- **ECDC.** European Centre for Disease Prevention and Control (Sweden)
- **EMA.** European Medicines Agency (United Kingdom)
- **EMC**. Erasmus Universitair Medisch Centrum Rotterdam (Netherlands) - Coordinator
- **GSK.** GlaxoSmithKline Biologicals, S.A. (Belgium) – EFPIA Coordinator
- **KI.** Karolinska Institutet (Sweden)
- **LSHTM.** London School of Hygiene &Tropical Medicine (United Kingdom)
- **OU.** The Open University (United Kingdom)
- **MHRA.** Medicines and Healthcare products Regulatory Agency (United Kingdom)
- **NOVARTIS.** Novartis Pharma AG (Switzerland)
- **PEDIANET.** Società Servizi Telematici SRL (Italy)
- **PFIZER**. Pfizer Limited (United Kingdom)
- **P95.** P95 (Belgium)
- **RCGP.** Royal College of General Practitioners (United Kingdom)
- **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu * National Institute for Public Health and the Environment (Netherlands)
- **SP.** Sanofi Pasteur (France)
- **SP MSD.** Sanofi Pasteur MSD (France)
- **SSI.** Statens Serum Institut (Denmark)
- **SURREY.** The University of Surrey (United Kingdom)
- **SYNAPSE.** Synapse Research Management Partners, S.L. (Spain)
- **TAKEDA**. Takeda Pharmaceuticals International GmbH (Switzerland)
- **UNIBAS**.Universitaet Basel (Switzerland) - **Managing entity of the IMI JU funding**
- **UTA.** Tampereen Yliopisto (Finland)
- **WIV-ISP.** Institut Scientifique de Santé Publique (Belgium)

- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ADVANCE project (115557).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The ADVANCE Consortium, comprising the above-mentioned legal entities.
- **Project Agreement.** Agreement concluded amongst ADVANCE participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

EXECUTIVE SUMMARY

As part of the IMI-ADVANCE project, a "Strategy for public communication in the context of vaccine benefit-risk monitoring" is to be developed (deliverable D.1.12.).

A key element for the development of communication recommendations is an analysis of issues and gaps that need to be addressed to improve the communication about vaccine benefit-risk (deliverable D.1.7.). For this purpose, listening to public concerns about vaccines is a necessary, but often neglected step in informing the development of a communication strategy. The working group has therefore focused this deliverable on a review of results obtained through listening to the public through media monitoring and use of social media. For completing deliverable D.1.7, this report presents the conclusions of the review to be taken into account for the strategy development.

The review covered background studies from IMI-ADVANCE partners and a pilot conducted at the EMA in 2015 for IMI-ADVANCE, involving real time news media monitoring to inform communication activities for an EU referral procedure on a vaccine safety concern (HPV vaccines).

The following recommendations are made:

- Benefit-risk assessment and communication should ensure the provision of responses to all safety concerns, including those debated in the public domain.
- Several strategies exist for listening to public concerns. Media and social media monitoring have emerged during the last decade thanks to increased technical capability to handle large volumes of data, and efficient media monitoring should be built into the process of vaccine benefit-risk monitoring.
- Media monitoring should support readiness for provision of proactive and responsive messages about vaccine safety, risks and risk minimisation.
- Media monitoring strategies restricted to news media seem to be sufficient at present for regulators to identify common information needs, but the development of the media landscape and journalism needs to be observed and might require opening routine monitoring of social media.
- Search strategies for media monitoring should include scientific, colloquial and brand names of the concerned vaccines.
- In order to use resources for global media monitoring efficiently, the number of languages for the content review should be limited to English and the languages of those countries with high media coverage of the relevant vaccine.
- Data about references in social media can be used to further identify news items that attract considerable public attention.
- Further work could go into developing hierarchical or conditional search algorithms to increase the specificity of search strategies without losing sensitivity.
- Future automated techniques for tone and topic analysis could increase the capacity and speed of media monitoring to allow for real-time analysis of public vaccine debates.
- Mechanisms for direct personal listening and interaction with stakeholders and public opinion leaders should be considered further as part of the strategy for public communication in the context of vaccine benefit-risk monitoring as an option, e.g. in the form of focus groups and media conferences. These relationships, once established, can later on be used for the trusted exchange over benefit-risk monitoring results.

- Efficient media monitoring should be built into the process of vaccine benefit-risk monitoring, and benefit-risk assessment should ensure the provision of responses to all safety concerns, including those debated in the public domain.
- Explanations on methods for benefit-risk monitoring and assessment should be provided in a language understandable to the public, and should be developed and ideally be tested with a view to explaining how the method works, what it can tell us, what its limitations are and how robust the results are.
- Given that conflicts of interests have been identified through the media monitoring as one of the biggest public concerns, the mechanisms of the public-private partnership (PPP) governance model, as envisaged by IMI-ADVANCE, and procedures to ensure unbiased benefit-risk monitoring and assessment need to be actively communicated to the public.

1. INTRODUCTION

As part of the IMI-ADVANCE project, a "Strategy for public communication in the context of vaccine benefit-risk monitoring" is to be developed (deliverable D.1.12.). As logical steps in the development of the communication strategy, two intermediate documents were developed by WG4 "Communication" of ADVANCE WP1:

- An analysis of public concerns and perceptions related to benefits and risks of vaccines; this document was submitted as deliverable 1.4;
- An analysis of key issues and gaps about perception and knowledge on benefits and risks of vaccines, which is included in this deliverable 1.7.

A key element for the development of communication recommendations is an analysis of issues and gaps that need to be addressed to improve the communication about vaccine benefit-risk. Module P.I of the European Union good pharmacovigilance practices (EU GVP) on vaccines for prophylaxis against infectious diseases, published in 2013, provides objectives and principles for communication on vaccines by marketing authorisation holders and national (regulatory) competent authorities [1]. It recommends that concerns raised by the public should be addressed by proactively communicating results of benefit-risk evaluations.

Listening to public concerns about vaccines is a necessary, but often neglected step in informing the development of a communication strategy. Listening to the public can involve different strategies. Besides traditional methods such as surveys or focus groups, advances in technology has facilitated the use of very large volume of data and increased the role of media and social monitoring. The working group has therefore focused this deliverable on a review of methods used to listen to the public through media monitoring and use of social media. This report presents the conclusions of the review to be taken into account for the strategy development.

This deliverable was planned to be submitted to IMI by month 24 of the project, i.e. September 2015. However, a media monitoring project was initiated by EMA in the context of a referral procedure on the safety of HPV vaccines (see Annex 4). This media monitoring took place from September to December 2015 and was considered an essential piece for this deliverable. It was therefore proposed to IMI to postpone it.

2. METHOD

The following background conducted by ADVANCE partners and IMI-ADVANCE studies were reviewed:

- Studies at Erasmus University:

- - Coloma PM, Becker B, Sturkenboom MC, van Mulligen EM, Kors JA. Evaluating social media networks in medicines safety surveillance: two case studies. Drug Saf. 2015; 38: 921-930. (Annex 1) (background) [2];
- - Becker B, Larson H, Bonhoeffer J, van Mulligen EM, Kors JA, Sturkenboom M. Evaluation of a multinational, multilingual vaccine debate on Twitter. [submitted for journal publication]. (Annex 2) (background) [3];

- Study at Sanofi Pasteur:

- Thomson A. Social media monitoring and vaccines, and a Mexican case study [presentation]. London: IMI-ADVANCE Work Package 1 Meeting; 11 December 2015. (Annex 3) (background) [4];

- Study at European Medicines Agency (EMA):

  - Bahri P, Fogd J, Kurz X. What the public wants to know about human papillomavirus vaccines: global media monitoring and coverage analysis using a 'virtual questions' approach. [to be submitted for journal publication]. (Annex 4) (study conducted under IMI-ADVANCE) [5].

3. RESULTS OF CASE STUDIES AND PILOT

3.1. Evaluating social media networks in medicines safety surveillance: two case studies

By Coloma PM, Becker B, Sturkenboom MC, van Mulligen EM, Kors JA (see Annex 1) [2]

This study evaluated the potential contribution of mining social media to capture patient-generated information relevant for medicines safety surveillance, on the basis of two case studies, i.e. rosiglitazone and cardiovascular events, and human papilloma virus (HPV) vaccine and infertility.

Publicly accessible, English-language posts on Facebook, Google and Twitter were collected up to September 2014. Messages were analysed with respect to geographical distribution, context, linking to other web content, and author's assertion regarding the supposed association.

A total of 2537 posts related to rosiglitazone/cardiovascular events and 2236 posts related to HPV vaccine/infertility were retrieved, with a high majority of posts representing data from Twitter and originating from users in the US. Approximately 21% of rosiglitazone-related posts and 84% of HPV vaccine-related posts referenced other web pages, mostly news items, law firms' websites, or blogs. Only ten posts described personal accounts of rosiglitazone/cardiovascular adverse event experiences, and nine posts described HPV vaccine problems related to infertility.

The study concluded that in these case studies publicly available data from social media were sparse and largely untrackable for the purpose of providing early clues of safety concerns, and that further research investigating other case studies and social media platforms are necessary to further characterise the usefulness of social media for safety surveillance.

3.2. Evaluation of a multinational, multilingual vaccine debate on Twitter

By Becker B, Larson H, Bonhoeffer J, van Mulligen EM, Kors JA, Sturkenboom M (see Annex 2) [3]

This study analysed Twitter messages in order to gain insight into international public discussion on the paediatric pentavalent vaccine (DTP-HepB-Hib) and vaccination programmes. This was considered important given that public confidence in these programmes is a pivotal determinant of its success and social media mining is increasingly employed to provide insight into public sentiment.

Using a multilingual search, all public Twitter messages mentioning the DTP-HepB-Hib vaccine from July 2006 until May 2015 were collected (5771 messages). They were analysed with regard to frequency of referencing other websites, type of websites, and geographic focus of the discussion. In addition, a sample of messages was manually annotated for positive or negative message tone, and this was combined with an automatic analysis of the geographical focus of messages over time.

Public messages about DTP-HepB-Hib were characterised by little interaction between tweeters, but frequent referencing of websites (news sites (70.7%), other social media (9.8%), and health-information sites (9.5%)). Many messages were comprised of only a reference or the title of the referred website, apparently being created by using functionality that is often embedded in web sites for "sharing" content on social media.

70.4% of the messages mentioned a country (India (35.4%), Indonesia (18.3%), and Vietnam (13.9%)). The debates were shaped by peaks of messages covering events in country-specific vaccination programmes, and the message authors were largely reacting to events in their own country or adjacent countries, suggesting rather multiple national debates than a multinational debate. Most messages were created by private persons and users representing and news sites. Stakeholders in the vaccination programme were overrepresented among the 50 users that created the largest number of messages.

There were almost no personal reports about the vaccine. Sharing of personal vaccine experiences and user interaction may be more common in private messages, but private messages were unavailable in this data set, given the focus of the study on messages which are made publicly viewable.

The debate was sharply polarised between messages proclaiming progress in the implementation of the vaccination programme and messages reporting suspected fatal outcomes of the vaccines. Few news articles reporting fatal outcomes of the vaccine adhered to the debate over a long period. In the annotated sample, 64% of the messages showed a positive or neutral sentiment about DTP-HepB-Hib.

The study concluded that Twitter messages reflect the public's awareness of major events in the debates about vaccines. Furthermore, monitoring and analysis of social media messages have demonstrated value. Continuous real-time monitoring of public debates about vaccines can support vaccination programmes by informing the programme of emerging issues, before they become crises that jeopardise public confidence in and acceptance of vaccines.

The study led to the recommendation that with automated techniques for tone and topic analysis, the capacity and speed could be improved for real-time analysis of public vaccine debates. Other suggestions for improving the monitoring strategy related to including more vaccine brand names in the search strategy and making the country allocation more accurate.

3.3. Social media monitoring and vaccines, and a Mexican case study

By Thomson A (see Annex 3) [4]

There are a number of levels of analysis and thus understanding that social media monitoring may provide, from monitoring channels using indicators such as topic, location, or sentiment, to in depth analyses of online social networks that may give insights into how conversations cluster and interact, and who is influencing them. In a joint project with Epidemico and Boston Children's Hospital, an open access dashboard, called the Vaccine Sentimeter, was developed to provide vaccination programme and communication managers with a tool to monitor and track the vaccination conversation in mainstream and social media [6] (see Annex 3). This system accesses and codes vaccination-related stories from over 50,000 sources including online news, blogs, expert-curated discussions, Twitter and validated official reports.

The Vaccine Sentimeter shows that the conversation in social media on vaccination is predominantly positive or neutral, and that social media is not highly trusted as a source of information on vaccination. Also there are not many signals of new safety concerns to be identified. However, it is important to

remember that sentiment measured by such screening tools does not necessarily correspond to actual human health behaviors. Any monitoring must be informed by good behavioural and social research to understand how and if indicators of topic, issues or sentiment online actually correspond to health behaviours.

3.4. What the public wants to know about human papillomavirus vaccines: global media monitoring and coverage analysis using a 'virtual questions' approach

By Bahri P, Fogd J, Kurz X (see Annex 4) [5]

This study at the European Medicines Agency (EMA) explored the utility of medicinal product-specific media monitoring for regulatory bodies, based on a pilot examining online news media about human papillomavirus (HPV) vaccines. The pilot was conducted from September to December 2015, to support a European Union (EU) referral procedure assessing potential causality of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS), both reported to the authorities as suspected adverse reactions.

The media monitoring occurred daily, covering worldwide online news media in most EU languages, and an analysis of topics, concerns and information gaps was performed weekly. Based on a cumulative review, the identified items were translated into 'virtual questions', i.e. questions which were raised in the media explicitly or implicitly, or topics which might not have be discussed if more information had been easily accessible in the public domain, or questions that could be anticipated to occur once more information would be provided. The virtual questions were formulated with terms commonly used in the regulatory and scientific environment.

About 60-100 news items were identified daily. The news items presented personal stories and over time increasingly included scientific and policy/process-related points. 50 virtual questions could be identified in 12 areas. At the EMA, this helped covering public concerns and information needs regarding CRPS and POTS by the assessment, impacted on the content and tone of public statements, and predicted all questions raised by journalists at the press briefing. It further helped the EU Member States' authorities in understanding their national communication demands in the global context.

The pilot study concluded that media monitoring has potential utility for regulatory bodies in their efforts to support trusted, safe and effective use of vaccines and that efficient media monitoring strategies could be part of a regulatory surveillance for medicinal products of high public health impact and/or high public interest. The potential utility consists of enabling the identification of main concerns and information needs of the public for proactively addressing these in widely disseminated summaries on assessment outcome and for preparing spokespersons for prompt responsiveness to most questions raised by journalists or others.

In order to use resources for media monitoring efficiently, the pilot experience suggested limiting the number of languages monitored to English and the languages of those countries with noted high media coverage of the medicinal product. The use of exclusion terms (e.g. budget, profit) to automatically rather than manually exclude financial or related news bears the risk that excluding articles about important policy and trust issues may be perceived as a bias given public expectations for independent data gathering and assessment. Further work could go into developing hierarchical or conditional search algorithms to increase the specificity of search strategies without losing sensitivity.

The results of the study lead to recommend the following principles and actions to improve communications on vaccine benefit-risk:

- Efficient media monitoring should be built into the process of vaccine benefit-risk monitoring, and benefit-risk assessment should ensure the provision of responses to all safety concerns, including those debated in the public domain.
- Explanations on methods for benefit-risk monitoring and assessment should be provided in a language understandable to the public, and should be developed and ideally be tested with a view to explaining how the method works, what it can tell us, what its limitations are and how robust the results are.
- Given that conflicts of interests have been identified through the media monitoring as one of the biggest public concerns, the mechanisms of the public-private partnership (PPP) governance model, as envisaged by IMI-ADVANCE, and procedures to ensure unbiased benefit-risk monitoring and assessment need to be actively communicated to the public.

4. RECOMMENDATIONS ON LISTENING AND MEDIA MONITORING

4.1. Discussion

The reviewed studies (see 3.) have come to similar conclusions. The results show that media monitoring relates less to identifying new safety concerns or their characteristics, but more to understanding vaccine sentiments, concerns, information needs and media behaviour of the public. This listening part of the communication process and subsequent increased understanding of public concerns and needs should facilitate that relevant concerns are addressed through proactive and responsive messaging about benefit-risk balances of vaccines. This messaging should aim to inform accurately and in a understandable manner about what is known and what is not known, rather than leaving confusion or rumour-provoking information gaps in the public domain.

While a lot about the communication ecosystem and the relationship between communication interventions and consequent behaviours still needs to be researched, it has been shown that the vast majority of online media activity about vaccines relates to re-distributing news rather than distributing original news. However, the selection of what gets re-distributed reflects public opinion or is influential in shaping public opinion. It has also been shown that the majority of the news is positive or neutral. It therefore seems appropriate to put efforts into communicating clear and honest messages in ways that they are heard, trusted and can be re-distributed.

Another aspect of the listening mechanism, in addition to media monitoring, is reviewing published research about vaccine risk perception and communication. Reviewing published research can contribute to obtaining insights in changes and trends in vaccine risk perception and communication. The IMI–ADVANCE deliverable D.1.4. "Analysis of public concerns and perceptions related to benefits and risks of vaccines" has provided a current picture of vaccine sentiments in Europe [7]. This can be used as a baseline for ongoing monitoring to understand which sentiments persist over time. As public trust can be destroyed very quickly, it is considered in this report that real time monitoring of public concerns and their impact on sentiments and behaviours is warranted.

The pilot project [5] demonstrated that media monitoring can be work intensive, and therefore media monitoring strategies have to be designed with efficiency in mind. For regulators to identify common information needs, a focus on news media may be appropriate at present.

The experience of the EMA has demonstrated the importance of formally collaborating with patient experts providing forums to listen to concerned patients. Examples relate to patient and user

perspectives on contraceptives and venous thromboembolism, valproates and congenital adverse effects and risks of certain treatments of multiple sclerosis [8]. Understanding and taking into consideration public concerns has impacted on regulatory decisions, risk minimisation measures and communication about risks. Welcoming patients in regulatory processes is also part of transparency and creates trust [9]. Direct interactions are of a value and solely monitoring the media or messaging via the media is not sufficient;this will be further considered in ADVANCE deliverable D.1.12.

4.2. Recommendations

The following recommendations on listening and media monitoring are made for the IMI-ADVANCE project and should be taken into account in the development of its "Strategy for public communication in the context of vaccine benefit-risk monitoring" (deliverable D.1.12):

- Benefit-risk assessment and communication should ensure the provision of responses to all safety concerns, including those debated in the public domain.
- Several strategies exist for listening to public concerns. Media and social media monitoring have emerged during the last decade thanks to increased technical capability to handle large volumes of data, and efficient media monitoring should be built into the process of vaccine benefit-risk monitoring.
- Media monitoring should support readiness for provision of proactive and responsive messages about vaccine safety, risks and risk minimisation.
- Media monitoring strategies restricted to news media seem to be sufficient at present for regulators to identify common information needs, but the development of the media landscape and journalism needs to be observed and might require opening routine monitoring of social media.
- Search strategies for media monitoring should include scientific, colloquial and brand names of the concerned vaccines.
- In order to use resources for global media monitoring efficiently, the number of languages for the content review should be limited to English and the languages of those countries with high media coverage of the relevant vaccine.
- Data about references in social media can be used to further identify news items that attract considerable public attention.
- Further work could go into developing hierarchical or conditional search algorithms to increase the specificity of search strategies without losing sensitivity.
- Future automated techniques for tone and topic analysis could increase the capacity and speed of media monitoring to allow for real-time analysis of public vaccine debates.
- Mechanisms for direct personal listening and interaction with stakeholders and public opinion leaders should be considered further as part of the strategy for public communication in the context of vaccine benefit-risk monitoring as an option, e.g. in the form of focus groups and media conferences. These relationships, once established, can later on be used for the trusted exchange over benefit-risk monitoring results.
- Efficient media monitoring should be built into the process of vaccine benefit-risk monitoring, and benefit-risk assessment should ensure the provision of responses to all safety concerns, including those debated in the public domain.
- Explanations on methods for benefit-risk monitoring and assessment should be provided in a language understandable to the public, and should be developed and ideally be tested with a

view to explaining how the method works, what it can tell us, what its limitations are and how robust the results are.

- Given that conflicts of interests have been identified through the media monitoring as one of the biggest public concerns, the mechanisms of the public-private partnership (PPP) governance model, as envisaged by IMI-ADVANCE, and procedures to ensure unbiased benefit-risk monitoring and assessment need to be actively communicated to the public.

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ANNEXES

ANNEX 1. Evaluating social media networks in medicines safety surveillance: two case studies

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Evaluating Social Media Networks in Medicines Safety Surveillance: Two Case Studies

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Abstract

Introduction There is growing interest in whether social media can capture patient-generated information relevant for medicines safety surveillance that cannot be found in traditional sources.

Objective The aim of this study was to evaluate the potential contribution of mining social media networks for medicines safety surveillance using the following associa- tions as case studies: (1) rosiglitazone and cardiovascular events (i.e. stroke and myocardial infarction); and (2) human papilloma virus (HPV) vaccine and infertility.

Methods We collected publicly accessible, English-language posts on Facebook, Google, and Twitter until September 2014. Data were queried for co-occurrence of keywords related to the drug/vaccine and event of interest within a post. Messages were analysed with respect to geographical distribution, context, linking to other web content, and author's assertion regarding the supposed association.

Results A total of 2537 posts related to rosiglitazone/cardiovascular events and 2236 posts related to HPV vaccine/infertility were retrieved, with the majority of posts representing data from Twitter (98 and 85 %, respectively) and originating from users in the US. Approximately 21 % of rosiglitazone-related posts and 84 % of HPV vaccine-related posts referenced other web pages, mostly news items, law firms' websites, or blogs. Assertion analysis predominantly showed affirmation of the association of rosiglitazone/cardiovascular events (72 %; $n = 1821$) and of HPV vaccine/infertility (79 %; $n = 1758$). Only ten posts described personal accounts of rosiglitazone/cardiovascular adverse event experiences, and nine posts described HPV vaccine problems related to infertility.

Conclusions Publicly available data from the considered social media networks were sparse and largely untrackable for the purpose of providing early clues of safety concerns regarding the prespecified case studies. Further research investigating other case studies and exploring other social media platforms are necessary to further characterise the usefulness of social media for safety surveillance.

Key Points

The growing popularity of online communities and social media networks is stimulating exploration of these sources for pharmacovigilance purposes.

The potential value of mining data from social networks appears to be greater for measuring awareness regarding emerging safety issues.

Further research investigating other case studies (including prospective investigations) and exploring other social media platforms are necessary to further characterise the usefulness of social media for pharmacovigilance.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-015-0333-5) contains supplementary material, which is available to authorized users.

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1 Introduction

The past decade has brought forth enormous growth and popularity of online communities and social networks, greatly expediting information exchange from one corner of the world to another. The concept of blogging has allowed virtually anybody with Internet access to post his or her views and

experiences on any topic at any time. Whilst the value of such online conversations has been exploited mostly by commercial enterprises to promote product improvement and innovation, healthcare has not been immune to this phenomenon of public engagement [1–3]. In the same spirit of eliciting greater patient par- ticipation, several investigators have begun to explore what social media can offer in terms of medicines safety surveillance [4–6]. Reporting of individual cases of sus- pected adverse drug reactions (ADRs) to regulatory authorities, mostly by physicians or other healthcare pro- fessionals, remains the cornerstone of pharmacovigilance. However, spontaneous reporting systems are hampered by various limitations, the most important of which is under- reporting [7, 8].

Because social media represent secondary data, i.e. data that are not originally intended for surveillance, there are challenges to overcome with respect to terminology, traceability and reproducibility. Apart from these technical challenges, practical policy guidelines are lacking on how potential safety signals from social media should be han- dled in the current regulatory framework. Although the US FDA has released two guidance documents on the use of social media platforms for presenting benefit/risk infor- mation on prescription drugs and medical devices [9], these documents are more concerned with product promotion than surveillance and "do not establish legally enforceable rights or responsibilities" [10]. The European Medicines Agency (EMA) guideline on good pharmacovigilance practices (Module VI) [11] provides provisions on how to deal with information on suspected adverse reactions from the Internet or digital media, and hold marketing authori- sation holders (MAHs) responsible for reviewing websites under their control for valid cases and reporting them accordingly, although there is no requirement to trawl Internet sites not under the control of the MAH. To date, there are no standard methodologies to mine user-gener- ated data from social media for pharmacovigilance. In this study we sought to evaluate the potential contribution of mining social media networks for pharmacovigilance using examples of drug–event associations that have been flag- ged as potential signals: rosiglitazone and cardiovascular events (i.e. stroke and myocardial infarction), and human papilloma virus (HPV) vaccine and infertility.

2 Methods

2.1 Data Sources

Postings were collected from three of the most widely used social media networking platforms (Facebook, Google?, and Twitter) using their respective search application pro- gramming interfaces (APIs). The search APIs return a set of public messages from the social network that match the query keywords. For each message the content is provided, together with additional information about the message itself (date and content), about the status in a conversation (repost or reply), and about the author (account name and location). The results are encoded in machine-readable format (Java- Script Object Notation [JSON]) for integration into custom application. Messages were obtained from as far back as available until 25 September 2014. Only English-language posts were considered. Facebook provides only messages from the preceding month using their search API, while the search API of Google? obtains messages dating back to its establishment in 2011. The search API of Twitter is restricted to a time window of approximately 1 week. In order to supplement the Twitter data obtained via its search API, an additional search engine, Topsy (http://topsy.com/) was used. Topsy is a real-time search engine for posts and shared content on social media, primarily on Twitter and Google?. Topsy has complete coverage of historical messages and has indexed every (public) tweet ever posted since 2006. As of this writing, Topsy was a Certified Reseller of Twitter's data. For this particular study, only Twitter-related posts were retrieved via the free analytics service of Topsy.com. No Facebook or Google? posts were retrieved in Topsy.

2.2 Case Studies

Usefulness of the above social media platforms for safety surveillance was evaluated using two examples of drug–adverse event associations that have previously been flag- ged as potential safety signals: (1) rosiglitazone and car- diovascular events (i.e. stroke and myocardial infarction); and (2) HPV vaccine and infertility. These two case studies were chosen because they represent associations that have triggered controversies and thus are likely to have been the subject of media attention as well as online discussions. Furthermore, the case studies involve different types of agents that are used by different subsets of the population under different circumstances, thus allowing investigation of diverse scenarios.

For each case study, data were queried for co-occur- rence of the drug/vaccine of interest and the event of interest within the same post or tweet. Search queries were

constructed using all possible drug–event keyword combinations (the keywords used are provided in the Appendix, available as electronic supplementary material). Event-related keywords consisted of clinical terms from the Unified Medical Language System (UMLS), as well as known abbreviations and layman's terms (see Appendix). Drug-related keywords consisted of international nonproprietary names and trade names.

2.3 Assessment of Suitability for Use in Safety Surveillance

Relevant posts were tallied and analysed with respect to geographical distribution, context, and linking to other web content. The country of origin of a message was automatically determined from the location information about the author. When the country was not available in a designated data field, it was manually identified from the available location information by means of a list of names of countries, regions and cities. The frequency of message propagation (i.e. reposts or retweets) was calculated. The content of all posts were reviewed one by one to determine whether there was reference to a person's actual experience of having the (adverse) event of interest in relation to exposure to the drug (or vaccine) of interest. It was not the intention to assign or assess causality, but rather to describe the context of how the drug–event relationship is described. Posts were likewise analysed with respect to the author's assertion of the purported association between the drug (or vaccine) of interest and the event of interest. Somewhat analogous to sentiment analysis, assertion was judged as one of the following: (1) 'affirmative', if the post alluded to an affirmation of the association; (2) 'negating', if the post alluded to a negation of the association; or (3) 'neutral', if the post alluded to neither affirmation nor negation of the association. Manual review and annotation of the assertions was undertaken by a physician/pharmacist (PMC). In addition, key dates during which important communication or regulatory actions occurred were marked and compared with the timeline of the posts.

3 Results

3.1 Rosiglitazone and Cardiovascular Events

As shown in Table 1, we retrieved a total of 2537 posts related to rosiglitazone and cardiovascular events (i.e. stroke and myocardial infarction), with the overwhelming majority of posts (98 %) representing data from Twitter. Only two posts were retrieved on Facebook, while 41 posts were retrieved on Google?. Approximately 10 % of all posts were reposts or retweets. The country of origin (based on the holder of the social network account) could not be automatically identified in 59 % of the posts; of the posts that could be identified, two-thirds were accounted for by the US, while the remaining one-third was distributed among 50 other countries or territories all over the world. Overall, 21 % of posts (n = 536) had links to other web pages (see Table 2). News items comprised more than one-third of the web pages referenced (n = 196), followed by law firms' websites or advertisements (n = 157) and blogs (n = 138). There were 24 posts referring to health information websites intended for health professionals, 15 posts linking to scientific journals, four posts referring to a patient community website, one post linking to a hospital's patient education website, and another linking to a You- Tube video.

Assertion analysis carried out on all posts predominantly demonstrated affirmation of the association between rosiglitazone and cardiovascular events (72 %; n = 1821), with the remainder more or less split between negating (13 %) and neutral (15 %). Most neutral posts were asking for further information or were otherwise not directly related to the drug–adverse event association. There were posts by lawyers or reporters explicitly soliciting cases (n = 12), but there were also posts (n = 122) ridiculing lawyers' television commercials that asked patients who 'died while taking the drug' to call a particular number. Figure 1 shows the trend of assertions over time in relation to events in the timeline of the association of interest. The highest peak of affirmative posts occurred in February 2010. In this particular month, the US Senate Finance Committee released a report based on a 2-year inquiry of rosiglitazone, expressing concern that the "FDA has overlooked or overridden safety concerns cited by its own officials" [12]. The EMA's suspension of rosiglitazone's marketing authorisation in the EU, and the FDA's restric- tion of access to the drug, coincided with the second peak of affirmative posts in September 2010, while the simul- taneous publication in high-impact journals of two studies demonstrating increased cardiovascular risk with the use of rosiglitazone [13, 14] coincided with the peak in June 2010. The peaks in negating assertions paralleled those of the affirmative, with the greatest peak in affirmations observed in June–July 2010 (and a smaller peak in November 2013), reflecting the active online debate that was happening regarding the issue. Figure 1 also shows that in June 2013, negating posts actually outnumbered the affirmative posts; the results of the FDA-mandated re- evaluation of the rosiglitazone (RECORD) trial [15] became available online in June 2013. The peak of neutral posts seen in July 2011 represented posts about news of rosiglitazone being potentially useful for neuropathic pain (although the pertinent study [16] had already been pub- lished online 3 months earlier).

Table 1 Overview of posts about rosiglitazone and cardiovascular adverse events across social media networking platforms

Social media	No. of posts (%)	No. of reposts (%)	No. of posts with links to other sites (%)	Earliest/latest date of retrieved	Origin of post (country, based on account holder)[a]
Facebook	2 (0.1)	0	2 (100)	July 2014/August 2014	US (1) Unknown (1)
Google?	41 (1.6)	6 (15)	41 (100)	June 2012/August 2014	Unknown (31) US (9) Egypt (1)
Twitter	2494 (98.3)	250 (10)	493 (20)	May 2007/September 2014	Unknown (1461) US (682) India (53) UK, Canada (50 each) Indonesia (31) Other countries (167)
Total	2537	256 (10)	536 (21)		

[a] Where applicable, only the top five countries are given

Table 2 Description of web pages referenced by posts about rosiglitazone and cardiovascular events

Category of linked web pages	Facebook [$n = 2$] (%)	Google? [$n = 41$] (%)	Twitter [$n = 493$] (%)	Total [$n = 536$] (%)
News	–	8 (20)	188 (38)	196 (37)
Law firm's website or advertisement	1 (50)	17 (41)	139 (28)	157 (29)
Blog	–	13 (32)	125 (25)	138 (26)
Health reference for professionals	–	2 (5)	22 (5)	24 (5)
Patient community	–	–	4 (1)	4 (\1)
website Health education	1 (50)	–	–	1 (\1)
Scientific journal	–	–	15 (3)	15 (3)
Video	–	1 (2)	–	1 (\1)

There were only ten posts that appeared to be about experiences of the drug–adverse event association of interest. Four posts involved the person posting the message himself or herself (one even claimed winning a legal case against the drug manufacturer); three involved somebody's brother-in-law, while there was one each for somebody's father, father-in-law, and grandmother. In addition, two posts referenced a patient community website that claimed 21,015 people reported to have had a heart attack while taking rosiglitazone (representing '32 % of all who reported side effects'). Interestingly, some posts ($n = 20$) alleged other adverse events of rosiglitazone, such as leg pain, abdominal pain and eye pain (all of which are symptoms suggestive of end-organ complications of diabetes, the primary indication for the drug), while others ($n = 67$) alluded to a beneficial effect of the drug (prevention of neuropathic pain).

3.2 HPV Vaccine and Infertility

A total of 2236 posts related to HPV vaccine and infertility were retrieved, again with the majority of posts (85 %) representing data from Twitter (see Table 3). There were 23 posts on Facebook, while 308 posts were retrieved on Google?. Reposts or retweets comprised 23 % of all posts. Similar to posts related to the previous case study on rosiglitazone, the country of origin was unknown for more than half of the HPV vaccine-related posts, with the US representing the majority ($n = 567$) of those posts that could be automatically identified. However, in contrast to the rosiglitazone-related posts, a large proportion of all posts (84 %) referenced other web pages (see Table 4). Various blogs comprised almost half of the linked web pages referenced ($n = 872$), followed by news items ($n = 669$) and scientific journals ($n = 118$). Most of the

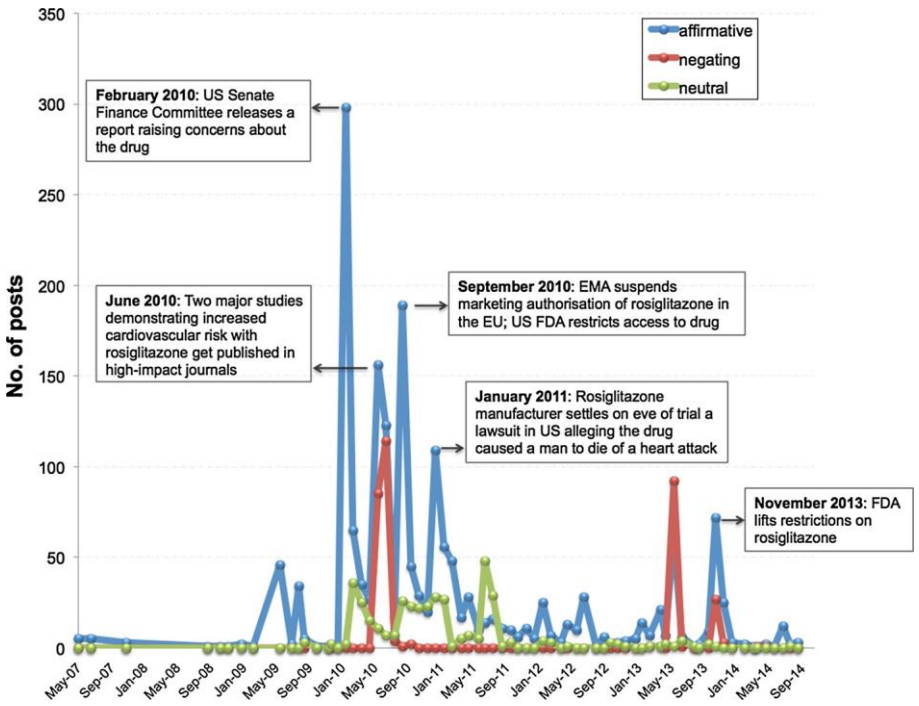

Fig. 1 Trend of assertions of rosiglitazone/cardiovascular event-related posts over time. *EMA* European Medicines Agency, *EU* European Union, *FDA* Food and Drug Administration

Table 3 Overview of posts about HPV vaccine and infertility across social media networking platforms

Social media platform	No. of posts (%)	No. of reposts (%)	No. of posts with links to other sites (%)	Earliest/latest date of retrieved post	Origin of post (country, based on account holder)[a]
Facebook	23 (1)	6 (26)	15 (65)	April 2014/September 2014	Unknown (19) Bangladesh, India, The Philippines, US (1 each)
Google?			308 (14)	67 (22)	286 (93)
September 2011/September 2014		Unknown (197)			
					US (61) Canada (7) Australia, India (6 each) UK (4) Other countries (27)
Twitter	1905 (85)	437 (23)	1570 (82)	July 2008/September 2014	Unknown (1059) US (505) Canada (112) Australia (40) UK (38) Italy, Egypt (10 each) Other countries (131)
Total	2236	510 (23)	1871 (84)		

[a] Where applicable, only the top five countries are given

blogs commented on these same news items or journal articles. There were 112 posts referring to health information websites intended for health professionals and 49 posts linking to (mostly antivaccine) YouTube videos, while only a minority of posts were associated with lawyer's websites or advertisements (n = 24).

The posts demonstrated predominantly affirmative assertion of the association between HPV vaccine and infertility (79 %; n = 1758), with posts that negate the association accounting for 4 % (n = 85) and neutral posts accounting for the rest. Most neutral posts were asking for further information (particularly with use of the vaccine

during pregnancy), were related to cervical cancer awareness, or were negative comments about the HPV vaccine in general but not directly related to infertility. Figure 2 shows the trend of assertions over time in relation to events in the timeline of the association of interest. The highest peak of affirmative posts occurred in November 2013 when two sisters, aged 20 and 19 years, alleged at a US federal court that Gardasil (trade name of the HPV vaccine) caused them to go into early menopause and become infertile. The build-up to this peak appears to have been triggered by a study describing three young women who presented with secondary amenorrhea following HPV vaccination [17]; this study was first published online at the end of July 2013 (corresponding to the earlier, but smaller, peak in Fig. 2). Many of the posts within the period from August to October 2013 actually referred to an event that happened 1 year before—the publication of the first case report on the association of interest. This case report of a 16-year-old Australian girl who had premature ovarian failure after HPV vaccination was first published online in October 2012 [18]. There were nine posts that appeared to be accounts of HPV vaccine–adverse event experience. Six posts involved the person posting the message herself. One simply said she was '15 and infertile' because of the vaccine (the actual page appears to have been taken down after the initial data collection), while four other individuals claimed to have an ovarian cyst, delayed period (and negative pregnancy test), (vaginal) spotting, menopause and hot flashes because of the vaccine. One post was about somebody's friend who was '21 and infertile due to the HPV vaccine' and there

Table 4 Description of web pages referenced by posts about human papilloma virus vaccine and infertility

Category of linked web pages	Facebook [n = 15] (%)	Google? [n = 286] (%)	Twitter [n = 1570] (%)	Total [n = 1871] (%)
News	4 (27)	126 (44)	539 (34)	669 (36)
Law firm's website or advertisement	–	3 (1)	21 (1)	24 (1)
Blog	5 (33)	111 (39)	756 (48)	872 (47)
Health reference for professionals	–	8 (3)	104 (7)	112 (6)
Scientific journal	–	1 (\1)	117 (7)	118 (6)
Video	1 (7)	16 (6)	32 (2)	49 (3)
Multiple sites, including health education	5 (33)	21 (7)	1 (\1)	27 (1)

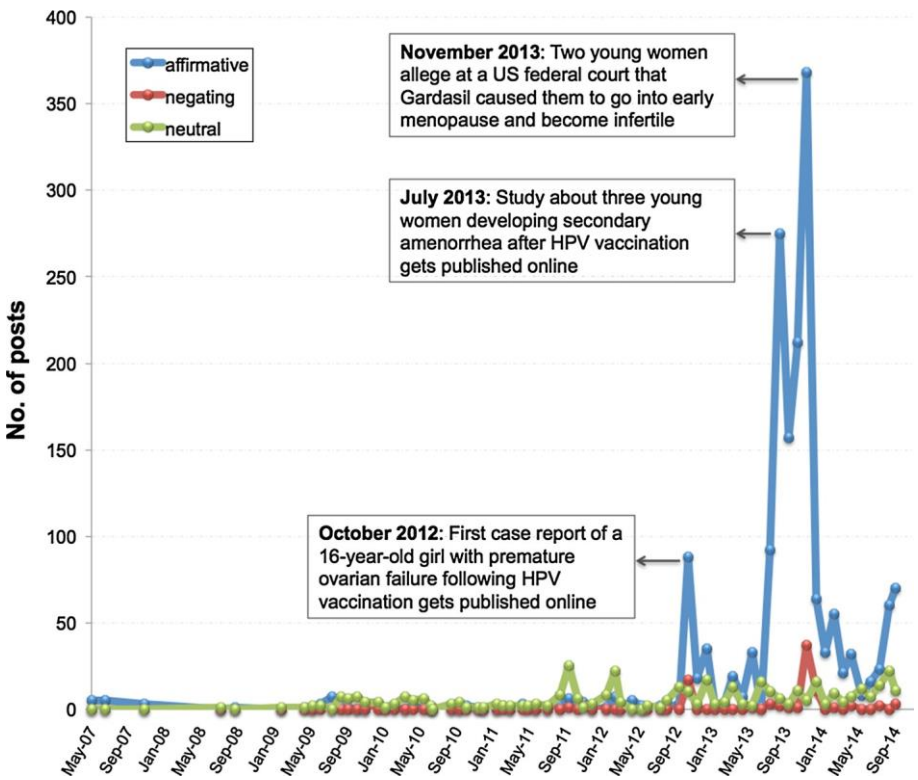

Fig. 2 Trend of assertions of HPV vaccine/infertility-related posts over time. *HPV* human papilloma virus

were two posts from different mothers whose daughters had no (menstrual) periods after receiving the vaccine.

4 Discussion

In this study, we aimed to characterise the data currently available from social media networking platforms and to determine if, and how, such data can be tapped for surveillance of two specific safety issues: rosiglitazone and cardiovascular events (i.e. stroke and myocardial infarction), and HPV vaccine and infertility. Rosiglitazone is a drug indicated for a very prevalent disease (diabetes), and although such a disease is expected to occur in the middle-aged population (who comprise a relative minority of the population of Twitter users), it was precisely one of the aims of this study to illustrate that such a group and such a condition of interest could be underrepresented in social media networks, however huge these networks may be. The primary motivation for exploring social media as an additional resource for pharmacovigilance is to capture information that cannot be found in traditional sources. Among the three websites evaluated, Twitter provided the greatest number of (publicly available) posts potentially relevant to the two case studies, but these mostly represented links to news items or, particularly for rosiglitazone and cardio- vascular events, websites of personal injury lawyers rather than accounts of drug/vaccine-related adverse events. The ubiquity and instantaneous nature of the Internet and social media networks supposedly provides a mechanism to find adverse drug (or vaccine, or medical device) experiences of laymen that are otherwise missed by ADR reporting systems, and in real time. Thus, one of the more relevant questions to ask is whether data from social media networks can provide early signs of potential safety concerns. Despite the hype about social media representing 'big data', the volume of relevant posts was sparse for the two case studies considered. Although Twitter has over 500 million users (more than half of whom are reportedly active), it was too 'young' a source to use, particularly for the case study on rosiglitazone. When the FDA issued the safety alert on Avandia in May 2007, Twitter had only been in service for less than 1 year, was largely in its trial phase, and thus still had few subscribers. The same argu- ment can be said for Facebook, which became available in September 2006, and Google?, which was launched much later in September 2011. The problem that these social media sites did not have enough time to accumulate data should have been less of an issue for the HPV vaccine–infertility association, which is a more recent potential safety concern, yet that does not seem to be the case.

Our findings corroborate what other researchers have shown regarding the geographic distribution of users of social media networks: a small number of countries, led by the US, account for a large share of the total user population and likewise make up the active and influential user population [19, 20] (see also http://www.beevolve.com/twitter-statistics/). Although this is not totally unexpected, given that only English-language posts were obtained in this study, there can be implications on inferences drawn from research using data from social media networks.

There were (only) 10 and 9 accounts of adverse experiences related to rosiglitazone/cardiovascular events and HPV vaccine/infertility, respectively, but these experiences appeared to be more reactionary than anticipatory (meaning they were shared online after news about the safety issues broke out). Furthermore, verification of such allegations proved to be difficult considering the data privacy constraints (only publicly accessible data could be analysed) and, in particular, establishing an identifiable patient and 'reporter' (required for valid safety reporting in traditional pharmacovigilance systems) is challenging, if not impossible. The scenario of unprincipled individuals spreading inaccurate, and even false, information is not unheard of [21], and since social media is largely unreg- ulated, cannot be avoided. Interestingly, two posts identi- fied in the current study referenced a health information and community website that claims to have studied (as of the time of writing this article) "65,460 people who have side effects while taking Avandia from FDA and social media", and among them, 21,015 had a 'heart attack' (http://www.ehealthme.com/ds/avandia/heart?attack). In addition, there were 7752 people who had a 'stroke' (http://www.ehealthme.com/ds/avandia/stroke). The website provides statistics on when the heart attack/stroke was reported, age and sex of people who had a heart attack/stroke when taking Avandia, 'time on Avandia when people have a heart attack/stroke', 'severity of the heart attack/stroke when taking Avandia', 'top conditions involved for these people', and 'top co-used drugs for these people'. All such information, if truthful, are relevant. However, nowhere is it stated which part of the information comes from social media and specifically from which social media (there are too many of them). More importantly, there is no description of how these reports were obtained, the actual configuration and content of the reports could not be traced, and the circumstances surrounding the alleged adverse events could not be verified. While the site does include a general disclaimer and a counsel to 'report adverse side effects to the FDA', these sections are found at the end of the page and may be easily ignored.

White et al. [22] utilised retrospective web search logs to make a case for Internet users providing early clues about adverse drug events via their online information seeking. Chary et al. proposed tools for using data from social networks to characterise patterns of (recreational)

drug abuse [23], while Harpaz et al. provided an extensive review on how state-of-the-art text mining for adverse drug events can leverage unstructured data sources, including social media [24]. Similar to the current study, Freifeld et al. used publicly available data from Twitter to obtain messages that resembled adverse event reports ('proto- AEs') related to 23 prespecified medical products [5]. Rather than focusing on a few specific events of interest, the Freifeld et al. study collected all potential events (symptoms), thus resulting in more permutations of search terms, which explains why their study had a higher yield of relevant posts compared with our study. While our current study was more of a 'scoping' study across three social media networking platforms for two specific case studies, the study by Freifeld et al. had a different aim—to evaluate concordance between Twitter posts mentioning AE-like reactions and spontaneous reports received by the FDA Adverse Event Reporting System. There is the implicit assumption of an equivalent level of information between the two sources, which, among other things, necessitated the development of a dictionary to map Internet vernacular
to the standardised ontology, Medical Dictionary for Regulatory Activities (MedDRA®). Other researchers have explored the utility of more specific health-oriented web-sites and patient community forums to identify adverse drug events [25] and to better understand the impact of ADRs [26]. These types of social media sources are likely
to provide more relevant content because their very nature allows for sharing of health-related concerns among patients with similar conditions ('like me') and would make verification easier since user registration is often mandatory and more exhaustive (the likelihood of faking an illness in this group is probably lower). Personal accounts of adverse events from such sources are often inaccessible to the public, although many of the prominent and moderated patient community websites will allow access to further information under certain conditions of use (and sometimes for a fee). These more health-oriented social media platforms are certainly worth exploring, especially for surveillance of uncommon adverse events, as well as those related to drugs indicated for rare conditions. The potential value of mining data from social networks appears to be greatest for measuring awareness regarding potential safety concerns. Because this study focused only on English-language posts, there is the caveat that the findings are biased towards users from English-speaking countries, particularly the US, which comprise the majority of subscribers of these social networking sites. Both number of posts and assertion trend in the two case studies were predominantly driven by events that occurred in the US. Another caveat is that bad news is often more popular than good news. The case report of the 16-year-old girl from Australia who had premature ovarian failure after HPV vaccination fired up huge comments online, while four studies (published earlier or around the same time) [27–30] that showed no evidence of increased risk for new adverse events, including those related to fertility, were practically ignored.

The other, perhaps even more relevant, question to ask is whether data from social media networks can be used to help corroborate, or refute, potential safety concerns by providing information where there is none. It is time to turn the impressionability of social media as an advantage and leverage it towards bringing balanced and evidence-based information to the Internet and its multitude of users.

Our study has several limitations. Data were queried for co-occurrence of the drug/vaccine of interest and the event of interest within the same post or tweet, which may have limited the number of relevant posts obtained. Similarly, the use of publicly available data and English-language- only posts may have contributed to sampling bias. The assertion analysis conducted may not always reflect the true opinion of the user, the very nature of social media promoting an open and unrestricted environment. A gen- eralisation cannot be made as to which among the social networking platforms provides the most valuable infor- mation since the amount and nature of commentaries generated and shared within each network is a function of its own culture and privacy restrictions. Moreover, the population of users of social networking sites comprises the relatively young (and healthy) and fairly educated who have access to the Internet [31–33]. The evaluation undertaken was retrospective and the findings for these particular case studies considered may not necessarily reflect discussions about safety concerns related to other drugs or other vaccines in the future. Because social media platforms are continually being re-engineered to improve the commercial service, there is the concern as to whether studies conducted on data collected from these platforms are reproducible, even 1 year later [34]. The phenomenon of 'blue team dynamics' has been described where the algorithm generating the data (and, consequently, user utilisation) has been modified by service providers such as Google, Twitter and Facebook in line with their business model [34, 35]. Similarly, there are the so-called 'red team' dynamics, which occur when social media platform users attempt to manipulate the data-generating process to sup- port their own economic or political gain [34, 36].

5 Conclusions

Publicly available data from the considered social media networks were sparse and largely untrackable for the pur-pose of providing early clues of safety concerns regarding the prespecified case studies (rosiglitazone and stroke/

myocardial infarction, and HPV vaccine and infertility). The potential value of mining data from social networks appears to be greater for measuring awareness regarding emerging safety issues, with the caveat that this will be biased towards a younger and healthier population who comprise the majority of subscribers of these social net- working sites. Further research investigating other case studies (including prospective investigations) and explor- ing other social media platforms are necessary to further characterise the usefulness of social media for postmar- keting safety surveillance.

Compliance with Ethical Standards

Only publicly available data were used in this study. No ethical approval or informed consent was necessary.

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Conflict of interest Preciosa M. Coloma, Benedikt Becker, Miriam C. J. M. Sturkenboom, Erik M. van Mulligen and Jan A. Kors have no conflicts of interest that are directly relevant to the content of this study.

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ANNEX 2. Evaluation of a multinational, multilingual vaccine debate on Twitter [draft]

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Abstract
Background
Public confidence in an immunization programme is a pivotal determinant of the programme's success. The mining of social media is increasingly employed to provide insight into the public's sentiment. This research further explores the value of monitoring social media to understand public sentiment about an international vaccination programme.

Objective
To gain insight into international public discussion on the paediatric pentavalent vaccine (DTP-HepB-Hib) programme by analysing Twitter messages.

Methods
Using a multilingual search, we retrospectively collected all public Twitter messages mentioning the DTP-HepB-Hib vaccine from July 2006 until May 2015. We analysed message characteristics by frequency of referencing other websites, type of websites, and geographic focus of the discussion. In addition, a sample of messages was manually annotated for positive or negative message tone.

Results
We retrieved 5771 messages. Only 3.1% of the messages were reactions to other messages, and 86.6% referred to websites, mostly news sites (70.7%), other social media (9.8%), and health-information sites (9.5%). Country mentions were identified in 70.4% of the messages, of which India (35.4%), Indonesia (18.3%), and Vietnam (13.9%) were the most prevalent. In the annotated sample, 63% of the messages showed a positive or neutral sentiment about DTP-HepB-Hib. Peaks in negative and positive messages could be related to country-specific programme events.

Conclusions
Public messages about DTP-HepB-Hib were characterised by little interaction between tweeters, and by frequent referencing of websites and other information links. Twitter messages can indirectly reflect the public's opinion of major events in the debates about the DTP-HepB-Hib vaccine.

Keywords
Vaccination programme; pentavalent vaccine; social media; vaccine debate; multilingual analysis

Introduction

Vaccination programmes are among the most effective means for improving population health. Particularly at the time of program introduction, they tend to be accompanied by public discussion [1,2]. This may increase public awareness of the vaccine and affect the programme beneficially [3]. However, public concern may lead to reduced uptake or even jeopardise the entire immunization programme [4,5]. Therefore, detecting changes in public sentiment early is important to understand its origin and dynamics and to inform appropriate measures to investigate concerns, guide public health decision making, or help identify issues with the vaccine or the vaccination programme.

Public attention and sentiment about vaccines have been evaluated previously by analysing different types of social-media messages and user-generated web content. Messages from the social-media platform *MySpace* were used for monitoring public sentiment about the human papillomavirus (HPV) vaccine [6]. Public news items about the HPV vaccine were shown to influence the public's awareness and opinion about HPV infection and vaccine in the United States [7]. Sentiments about an influenza vaccine shared through Twitter messages were found to correlate highly with US vaccination rates as reported by the Centers for Disease Control and Prevention [8]. International debates about vaccines and the course and drivers of public confidence have also been studied through analysis of media sources such as news sites, blogs, and governmental reports [2,9]. Twitter and other social media have frequently been used for post-marketing surveillance of pharmaceutical safety issues [10–12]. Some studies have concluded that monitoring social media is more suitable for measuring public awareness of known safety issues than for providing clues about new safety signals [13].

Since 2001, a pentavalent paediatric vaccine against Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenzae type b (DTP-HepB-Hib) has been introduced into more than 70 low- and middle-income countries (LMICs) [14]. In a number of countries, the introduction of the vaccine was accompanied by a critical debate following a suspected association with the death of children, none of which have been deemed as causally related to the vaccine [15]. In India, a petition and a lawsuit was filed against the vaccine [16,17]. In Sri Lanka, Bhutan, and Vietnam, the market authorisation for the vaccine was even temporarily suspended [18].

In this study, we explore the value of public Twitter messages to gain insight into the multinational debate on the pentavalent vaccine.

Methods

Data collection

We used Twitter's advanced search web interface to collect messages retrospectively. The messages were collected on 1 May 2015. The advanced search interface provides the content and date of messages from the entire history of Twitter since 2006. We queried Twitter's web API (application programming interface) to retrieve additional data fields describing the language of the content, the identity of the author, the geographical location in his or her user-profile, and the interaction status of the message (original post, repost, or reply).

The search query *"pentavalent OR pentavac OR quinvaxem"* was used to retrieve messages about the pentavalent vaccine. The query terms were selected to retrieve messages from multiple national discussions about the vaccine, but not from all national or language-specific discussions (which would have required, amongst others, the inclusion of country-specific brand names and slang terms). The terms *"pentavac"* and *"quinvaxem"* are brand names of the pentavalent vaccine and specific to the vaccine as such. The term *"pentavalent"* is also used in various other contexts (e.g., "pentavalent" is used in chemistry and as user name on Twitter). To remove unrelated messages, a message retrieved by the term "*pentavalent*" was only retained if it also contained the term "child" or "vaccine" (in the language of the message). The terms for *child* and *vaccine* in different languages were retrieved from OmegaWiki (http://www.omegawiki.org), a community-driven, multilingual dictionary. *OmegaWiki* provided 94 terms for *child* and 45 terms for *vaccine*. The terms came from 67 different languages.

Message analysis

A random sample of 10% of the messages was selected for manual analysis. The message tone was manually analysed to gain insights into the sentiment about the pentavalent vaccine as reflected on Twitter. The two categories of message tone – *positive/neutral* and *negative* – and the criteria to assign the categories were the same as previously described [9]. A message was coded *negative* if it contained any indication of concern about the pentavalent vaccine or vaccination programme, e.g., information about an adverse event that occurred after immunization, vaccine suspension, or any other factor that

might have a negative effect on the vaccine programme. A message was coded *positive/neutral* if it contained no indication of public concern about the vaccine or vaccination programme. Non-English messages were translated with Google Translate (https://translate.google.com) while annotating. Google Translate covered the languages of all messages in the sample, and the tone was apparent from the translations for all messages.

All authors of the messages in the random sample and the 50 authors creating most messages overall were characterized as *private person*, *news site*, *health information*, *health organization*, *government*, vaccine-critical, *manufacturer,* or *non-governmental organization (NGO)* based on their public Twitter profile.

To characterise the use of references in the collected messages, the most commonly referred (top-level) web domains were categorised as *news site*, *social media, health information, health organisation,* and *other*. Additionally, all messages from the random sample that contained references, were manually assessed if the author added own content (i.e., if the message contained more than a link to or the heading of the referred website).

We defined the geographical focus of a message by identifying the countries mentioned in the message or referred web pages. A dictionary of terms for geographical entities of countries (including cities and regions) was compiled from the *GeoNames* database (http://geonames.org) to identify mentions of countries automatically. To disambiguate terms that referred to entities in different countries, the country with the entity that had the largest population was selected. For example, *Bali* is the name of a city in India and an island in Indonesia in the *GeoNames* database. Because the population of the Indonesian island is larger than that of the Indian city, mentions of Bali were assigned to Indonesia. Messages that contributed to peaks in the message distribution over time were manually reviewed to identify the events that triggered the peaks.

The messages were analysed for occurrences of the standard format for reposts (*"RT @user"*) to complement the information provided by the Twitter API. However, when evaluating public awareness and sentiment we did not distinguish between original posts and reposts, assuming that users primarily repost messages that reflect their own stance.

Results

We retrieved 7657 messages about the pentavalent vaccine from Twitter, of which 5771 (75.3%) from 2945 users remained after disambiguation. The number of messages grew over the years from 10 messages in 2008 to 2619 messages in 2013 (32 in 2009, 110 in 2010, 446 in 2011, and 1033 in 2012). The numbers of messages should be seen against the background of a strong growth of Twitter messages until 2012, as well as the expanded introduction of the pentavalent vaccine and incidents of public resistance in some countries. After 2013 the number of messages declined (1091 in 2014 and 430 until May 2015). A histogram of all messages per month from 2012 until May 2015 is shown in figure 1a.

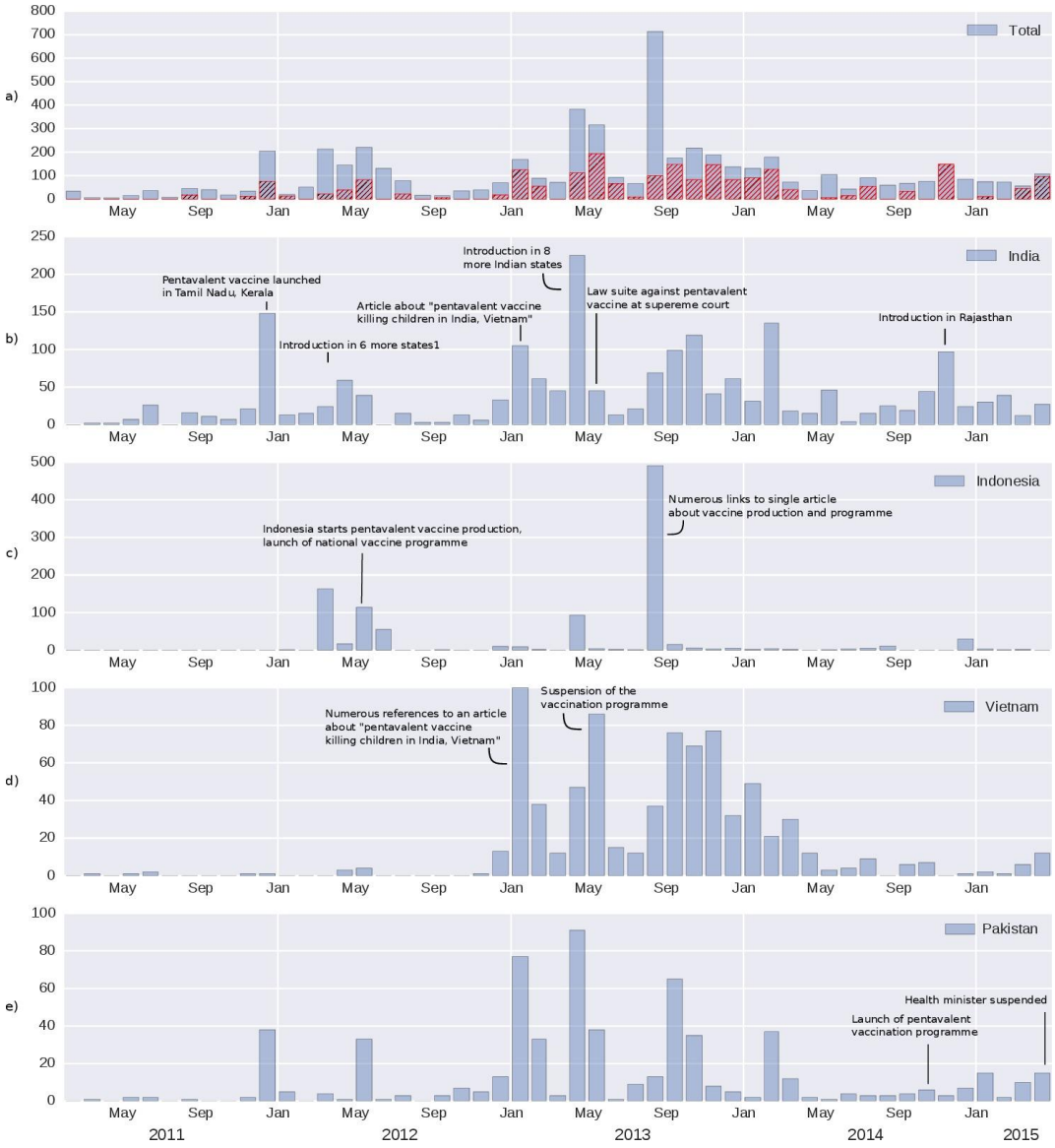

Figure 1: Number of messages about the pentavalent vaccine from January 2011 until April 2015 by month, with the estimated portion of messages with negative tone as striped bars. (a) All messages, (b) India, (c) Indonesia, (d) Vietnam, (e) Pakistan. Messages between 2008 and 2010 (152; 2.6%) are not shown for clarity of the figure.

In the manually annotated sample of 585 messages, 9 messages (1.5%) were false positives of the message retrieval and filtering and unrelated to the pentavalent vaccine. Among the 576 messages referring to the pentavalent vaccine, 37% had a *negative* tone and 63% of the messages had *positive/neutral* tone. The striped bars in figure 1a show the estimated number of messages with negative tone. No personal experience reports with the vaccine were found in the manually annotated messages.

Figure 2 shows the distribution of users from the random sample and of the top-50 tweeters over the user categories. In both sets most users are private persons or represent news sites. Health information sites, health organizations (including Global Alliance for Vaccines and Immunization (GAVI), World Health Organization, and CDC), governments, and vaccine-critical forums were overrepresented among the top-50 users. Many users (1979; 67.2%) created only a single message, 920 users (31.1%) created 10 or less messages and the 50 users with the largest number of messages (1.7%) each created between 10 and 113 messages.

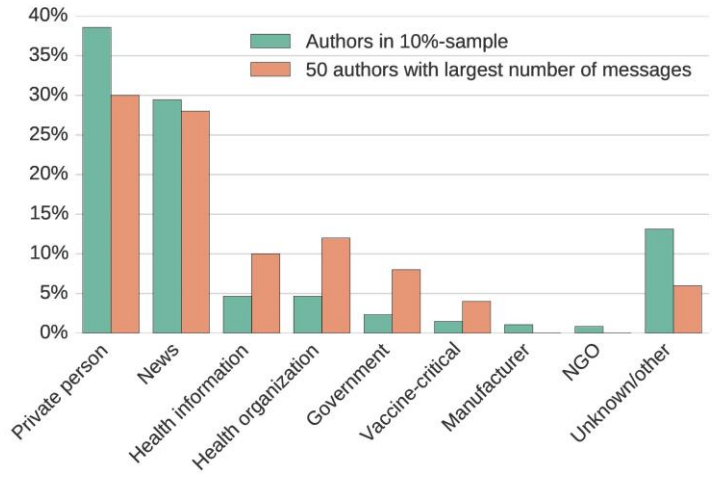

Figure 2: Distribution of users in the random sample and of the 50 users who created the largest number of messages, over different user categories.

The dictionary of geographic entities contained 19096 terms for 246 countries in 125 languages, with a median of 51 terms per language. In total 135 terms (0.7%) referred to entities in different countries and were disambiguated by population size. After a preliminary identification of countries, 78 terms were removed from the dictionary because the terms did not refer to geographical entities. Overall, 149 different countries were identified in 4067 (70.4%) of the messages. The most frequently mentioned countries were India (2047; 35.4%), Indonesia (1056; 18.3%), Vietnam (803; 13.9%), and Pakistan (631; 10.9%). Most countries (104) were identified in less than 1% of the messages.

The most common languages of the messages were English (61.3%), Indonesian (16.1%), and Vietnamese (7.1%). English occupies a special role as the most common language on Twitter and as a common language for public communication in India. Countries were most frequently detected in Indian messages (79.2%), English messages (60.0%), French messages (44.4%), and Vietnamese messages (35.0%). Multiple countries were mentioned in 36.9% of the messages.

The country of origin could be identified by the information about the author for 3067 (53.1%) messages. Most authors came from India (849; 27.6%), Indonesia (505; 16.4%), United States (458; 14.9%), and Vietnam (267; 8.7%). The relationship between the country of the message author and the country mentioned in the message content is shown in figure 3. Each cell contains the proportion of messages by users from the country on the row, which mention the country in the column. The figure shows that authors largely focus on their own or adjacent countries. Most messages from the United States, which contributes the largest number of Twitter users but where the pentavalent vaccine was not introduced, refer to events in India.

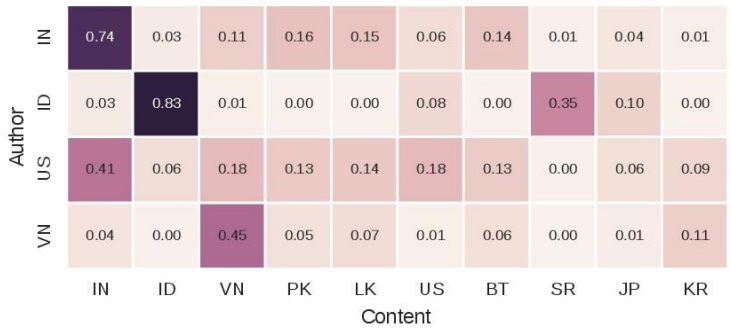

Figure 3: The relationship between the country of the message author (vertical axis) and the country that is mentioned in the message (horizontal axis). Each cell contains the proportion of messages by users from the country on the row, which mention the country in the column (e.g., 74.3% of the messages from users in India are about India).

Only 158 messages (2.7%) were replies to other messages, and 180 messages (3.1%) were reposts. References to websites were very common, as 86.6% of the messages contained at least one reference. In the manually annotated sample, the users provided original content in only 15.2% of the messages. The remaining messages only contained a link or copied content of the referred page. The most frequently referenced web domains were newspapers (70.7%), other social media (9.8%), health information sites (9.5%), and health organisations (9.3%).

Most peaks of messages in figure 1a could be broken down to peaks of messages in individual countries, which in turn were in temporal relation to country-specific events as annotated in figures 1b-e. Messages from India in December 2011 discussed the introduction of the pentavalent vaccine in the states Tamil Nadu and Kerala, and in May 2012 the introduction in five other states. The discussion about the vaccine gained momentum in India in 2013. Messages in January 2013 referenced news articles about child fatalities supposedly related to the pentavalent vaccine. The messages in April 2013 discussed the introduction of the pentavalent vaccine in eight more Indian states, but also criticized a supposed re-labelling of expired vaccines. The discussion in August-October 2013 included voices demanding the ban of the vaccine and continued discussions about the child fatalities. Numerous messages from February 2014 referred to articles alleging the association of the vaccine with child fatalities. Messages from May 2014 referred to the prequalification of a new brand of the pentavalent vaccine by the WHO. The messages from October/November 2014 discussed the introduction of the vaccine in the state of Rajasthan. Numerous news items in January, April, September and October 2013 primarily addressed the vaccination programme in India but also mentioned the vaccination programmes in Vietnam, Pakistan, and Sri Lanka, resulting in message peaks in the latter countries.

The messages about Indonesia in March 2012, August 2013 and December 2014 were composed of references to a few news articles discussing the production and introduction of the pentavalent vaccine in Indonesia. The messages in May 2013 discussed the suspension of the vaccination programme in Vietnam. Messages about Vietnam in November 2013 referred mainly to news items alleging (severe) adverse effects of the vaccine. In Pakistan the pentavalent vaccine was introduced in late 2014 and the November messages reference news articles about the introduction. The messages from Pakistan in March 2015 discussed the suspension of a health official for having spoiled the national pentavalent vaccine supply due to inappropriate storage.

Discussion

In this study, we conducted an analysis of Twitter messages to characterize multinational debates about the pentavalent vaccine and vaccination programmes. We combined an analysis of geographical focus of the messages and message tone over time.

The debates on Twitter were shaped by peaks of messages covering events in country-specific vaccination programmes. The perceptions of events on Twitter were local: authors of messages were largely reacting to events in their own country or adjacent countries, suggesting multiple national debates rather than *a* multinational debate. The debate was highly polarized between messages indicating that the vaccine (programme) was saving children's lives or killing them. In contrast to a previous study that observed a broad variety of concerns about vaccines in news sites, blogs and governmental reports [9], the dominant concern in our data was about the safety of the vaccine. Most messages were created by private persons and users representing and news sites. Stakeholders in the vaccination programme were overrepresented among the 50 users who created the largest number of messages.

The Twitter messages had three salient properties that have also been observed in other domains [13]: few interactions (replies, reposts) between users, virtual absence of personal reports (in our case about the vaccine), and frequent references to other websites, particularly news portals. Many messages were comprised of only a reference or the title of the referred website. This appears to indicate that the messages were mainly created to share content on social media rather than to communicate with other users in the social network, a pattern that was also observed in Twitter messages about a Measles vaccine in the Netherlands [19]. These properties can at least partially be explained by the focus of this study on messages which are made publicly viewable. Sharing of personal vaccine experiences and user interaction may be more common in private messages, but private messages were unavailable in our data set.

With the lack of personal reports about the vaccine, our data does not directly reflect the public's opinion about the vaccine (programme). But the Twitter messages reflect the users' opinion indirectly: The majority of messages were created by sharing web content among connected Twitter users, and the fact that no proper content was added by the authors of most messages suggests that the author

concurs with the referenced content and sentiment towards the vaccine. The question whether messages on Twitter can shape public opinion was not in the scope of this article but other studies argue that clear and transparent communication about vaccines, e.g., through social media like Twitter, can improve uptake rates [1,3].

The analysis of Twitter messages for evaluating public sentiment constitutes a bias towards a debate between relatively young people with internet access instead of the general public [20]. But this age group corresponds to young parents who decide the administration of the pentavalent, paediatric vaccine. And while most Twitter users are from the United States, many countries where the pentavalent vaccine has been introduced are among countries with the highest number of Twitter users [21].

Our study has some methodological limitations. First, the pentavalent vaccine has been marketed with various other brand names that were not used as query terms in this study. The inclusion of further brand names into the search query could help expanding the study to more countries where there are national debates about the vaccine (e.g., the scope of the study could be expanded to the vaccination programme in Ukraine by including the local brand name *Пентаксим*). However, we do not expect the characteristics of Twitter messages as described above to differ strongly in other countries. Second, the disambiguation of terms for countries based on population sizes may result in misallocations and could be improved by taking the context of the mention in the message into account. Third, we automatically detected countries in messages, but did not try to determine whether a country mention was vaccine-related. The analysis of geographical focus in the debate could be refined by distinguishing between country mentions that are related to the vaccine and those that are not.

Conclusion

The continuous monitoring of public debates about vaccines can help to alert vaccination programmes to emerging issues that cause public confidence to plummet. We showed the potential value of monitoring social media retrospectively based on manual analysis of messages. When applying automatic techniques for the analysis of tone and topic of messages, the approach presented could increase the capacity and speed to allow for real-time analysis of public vaccine debates.

Disclosure

This project was partially funded by WHO project SPHQ13 - LOA 209.

BB conceptualized the study, retrieved and analyzed the data, and drafted the manuscript. HL, JB, EM, JK, and MS conceptualized the study, and reviewed and revised the manuscript. All authors approved the final manuscript.

Conflicts of interest: none.

Only publicly available data were used in this study. No ethical approval or informed consent was necessary.

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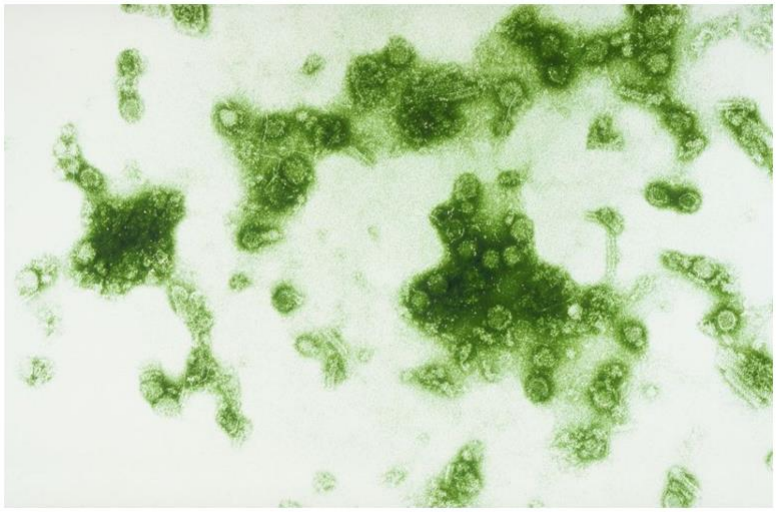
ANNEX 3. Social media monitoring and vaccines, and a Mexican case study

Thomson A. Social media monitoring and vaccines, and a Mexican case study [presentation]. London: IMI-ADVANCE Work Package 1 Meeting; 11 December 2015.

Slide 1

Slide 2

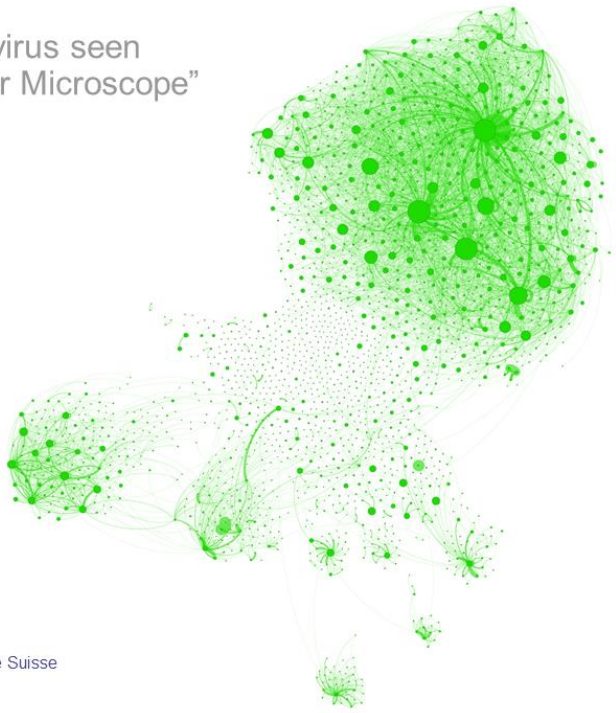
Dengue virus seen under an electron microscope



Photographer: Institut Pasteur
Copyright: Sanofi Pasteur

Slide 3

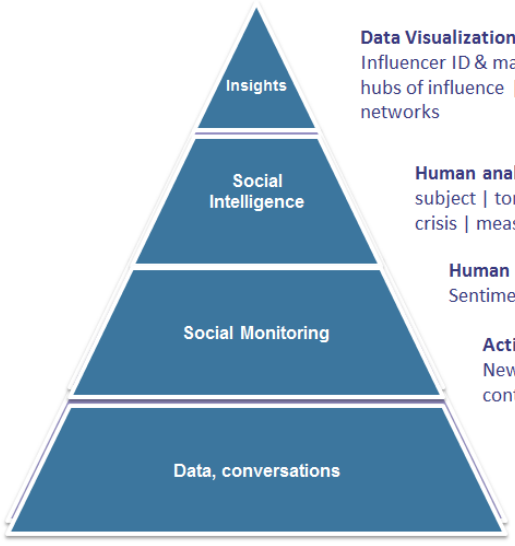
Dengue virus seen
under “Twitter Microscope”



Data viz: Stephane Suisse

Slide 4

Listening & understanding:
From Raw Data to Social intelligence



Data Visualization (networks):
Influencer ID & mapping
hubs of influence | Social networks

Human analysis (drill down):
subject | tone | buzz
crisis | measure & evaluate

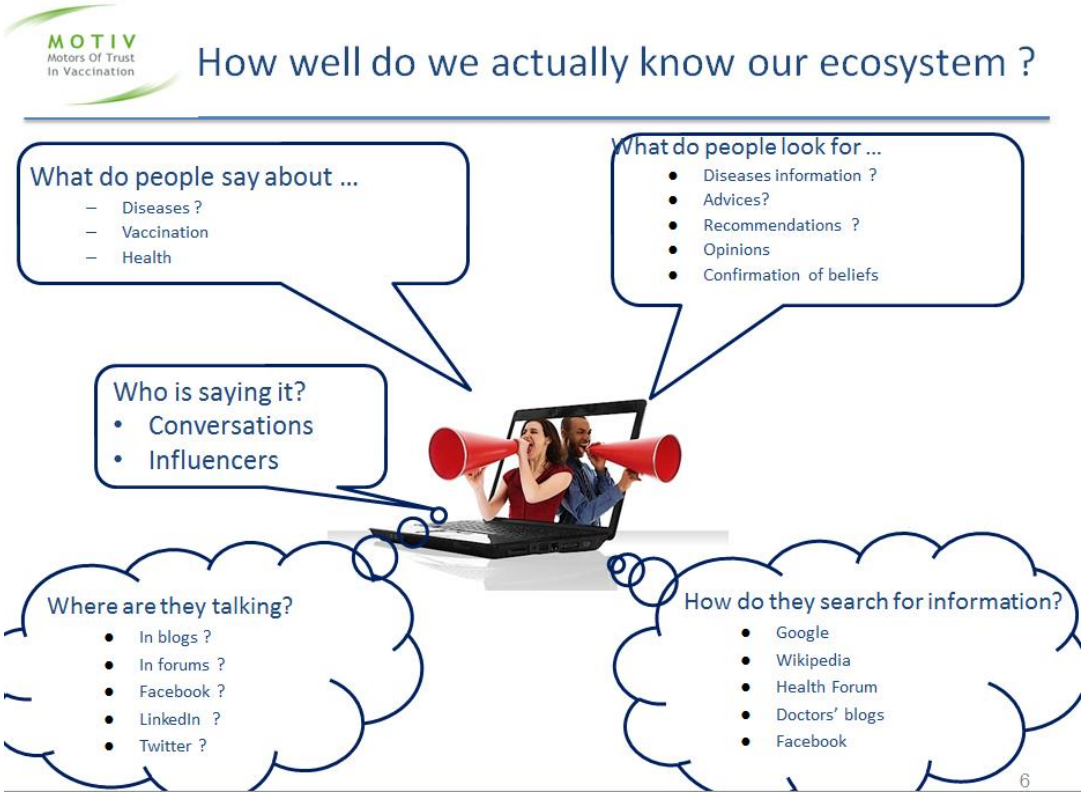
Human analysis (to refine algorithms):
Sentiment | topic | buzz |

Active surveillance (events):
News | rumors | issues
controversies | outbreaks

Monitoring (indicators):
Volume | channel | sentiment
topic | region | language

Slide 5

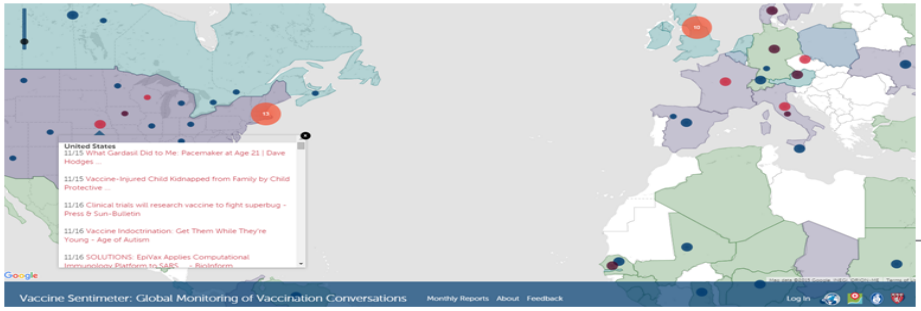
Slide 6



Slide 7

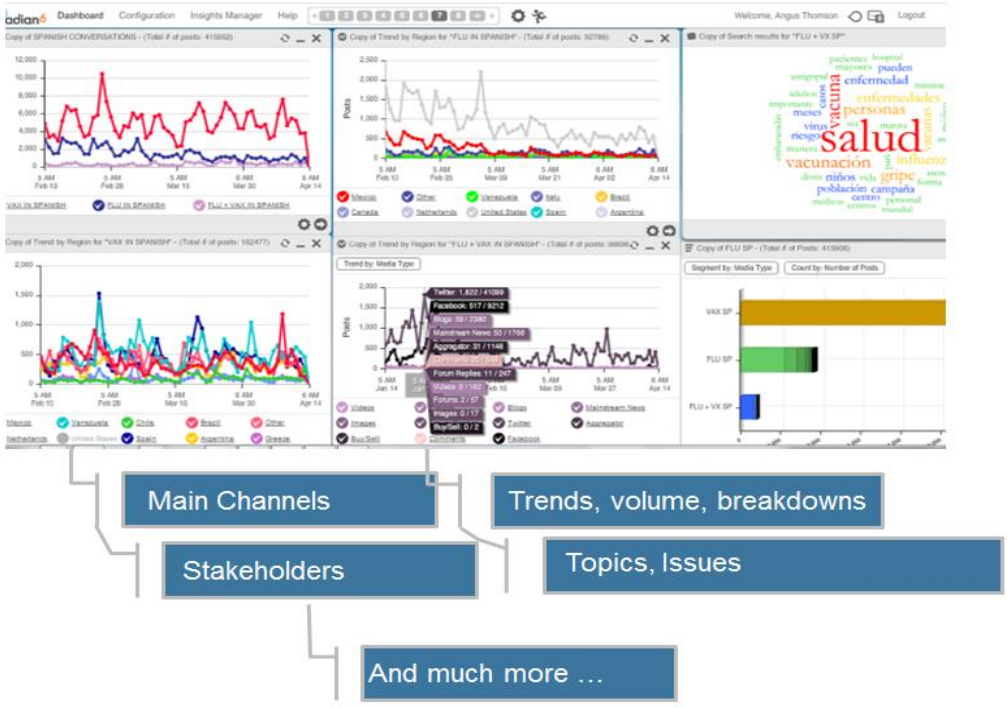
Monitoring the online vaccination conversation

- Open access dashboard
- Aim: to give vaccination program and communication managers a open tool to monitor and track the conversation in mainstream and social media on vaccination
- Vaccination-related stories from 50,000+ sources including online news, blogs, expert-curated discussions, twitter and validated official reports.
- Public health experts at ProMED and Epidemico curate the web & social media data.
- Developed by HealthMap & Sanofi Pasteur
- Currently in beta, but available now online
- Currently looking for partners to help develop it, including adding new languages



Slide 8

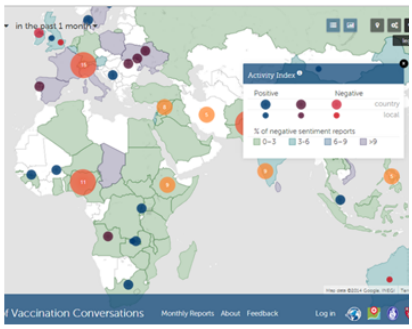
Monitoring - 2



Slide 9

Understanding the vaccination conversation in social media

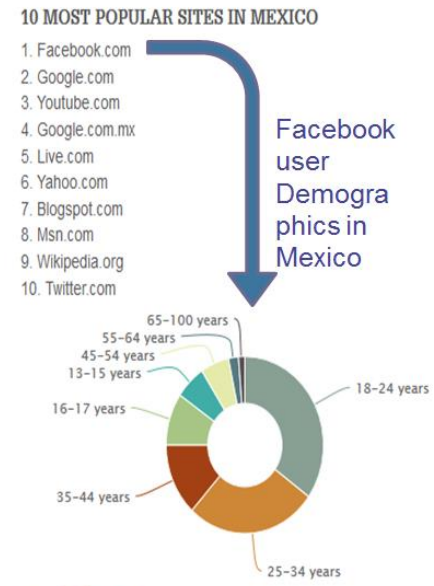
- The conversation in social media on vaccination is predominantly positive or neutral
- Social media is not highly trusted as a source of information on vaccination [1]
- There are not that many signals
- We cannot understand health behaviors with any reliability - yet



1. unpublished data from a 5-country study

Slide 10

Mexico case study: Digital usage



Source: socialbakers

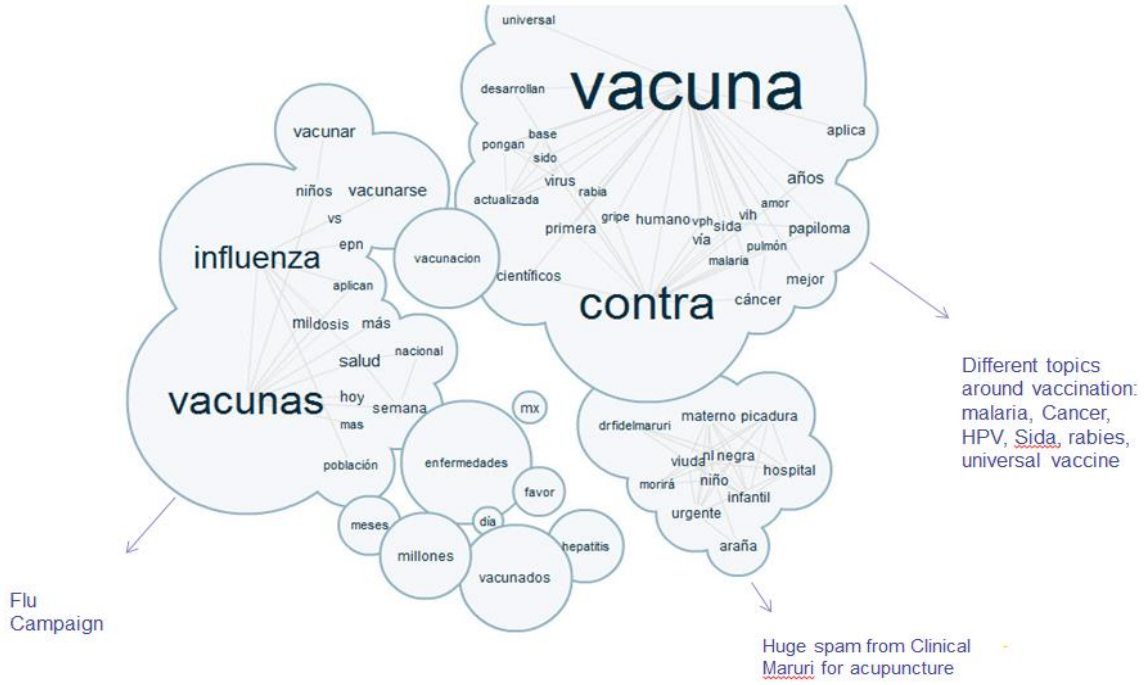
Most Popular Audience Interests include:

- Arts and Entertainment
- Urban & Hip-Hop
- How-to
- DIY
- **Expert Content**

Source: www.mvfglobal.com/mexico

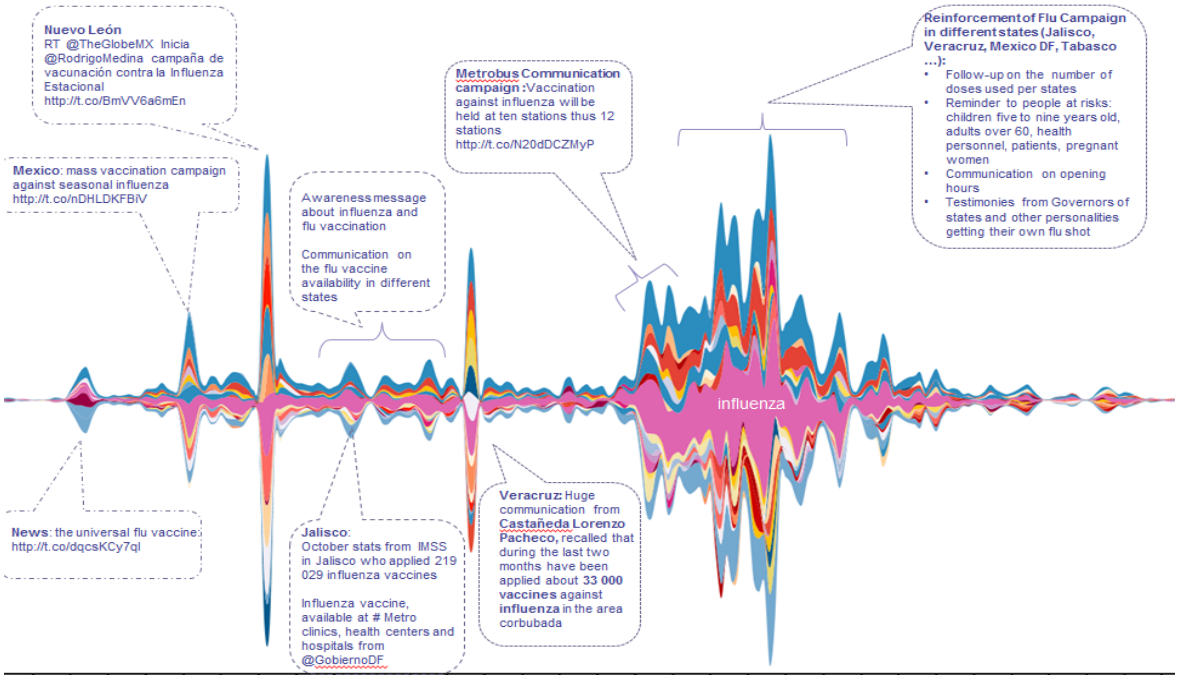
Slide 11

Mexico case study: Topics

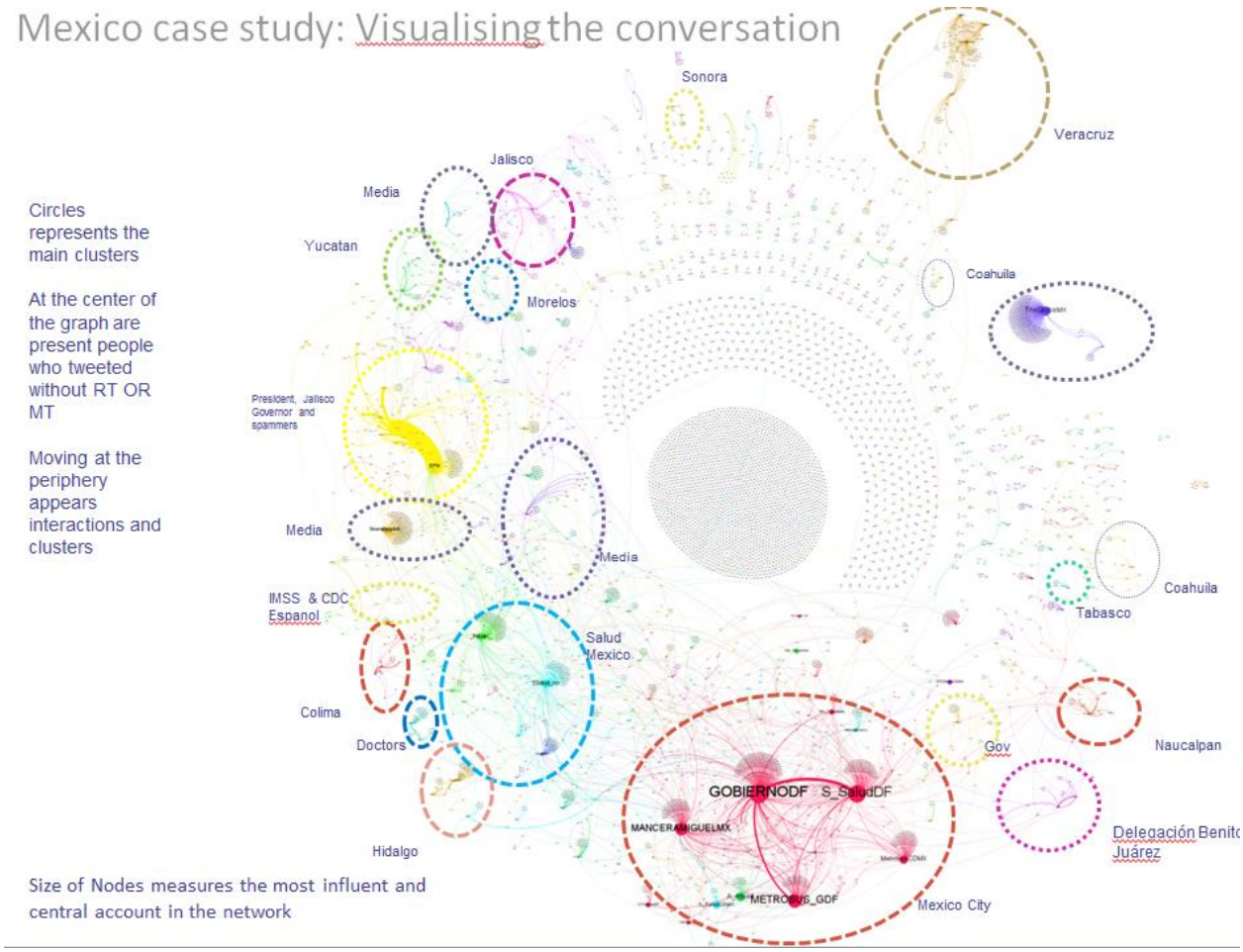


Slide 12

Mexico case study: tracking the flu campaign



Slide 13


Mexico case study: Visualising the conversation
Circles represents the main clusters
At the center of the graph are present people who tweeted without RT OR MT
Moving at the periphery appears interactions and clusters
Size of Nodes measures the most influent and central account in the network
Sonora
Veracruz
Jalisco
Media
Yucatan
Morelos
Coahuila
President, Jalisco Governor and spammers
Media
Media
IMSS & CDC Espanol
Salud Mexico
Colima
Doctors
Hidalgo
Tabasco
Coahuila
Gov
Naucalpan
GOBIERNODF
Delegación Benito Juárez
Mexico City

Slide 14

Applying S2M to vaccine risk detection & responses

- Listening
  - Signal detection
  - Signal characterisation
- Understanding
  - In-depth analyses
- Engaging
  - Risk communication principles
  - Address specific concerns?
  - Mobilizing & equipping influential voices

The feeling of risk
In risk communication, the *how* is more important that the *what*

Slide 15

MOTIV
Motors Of Trust In Vaccination

Risk

- The feeling of risk
- Risk = hazard + outrage

- In risk communication, the *how* is more important that the *what*

Social media monitoring – Angus Thomson

By Chi Y. Bahk, Melissa Cumming, Louisa Paushter, Lawrence C. Madoff, Angus Thomson, and John S. Brownstein

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HEALTH AFFAIRS 35,
NO. 2 (2016): 341–347

Publicly Available Online Tool Facilitates Real-Time Monitoring Of Vaccine Conversations And Sentiments

ABSTRACT **Real-time monitoring of mainstream and social media can inform public health practitioners and policy makers about vaccine sentiment and hesitancy. We describe a publicly available platform for monitoring vaccination-related content, called the Vaccine Sentimeter. With automated data collection from 100,000 mainstream media sources and Twitter, natural-language processing for automated filtering, and manual curation to ensure accuracy, the Vaccine Sentimeter offers a global real-time view of vaccination conversations online. To assess the system's utility, we followed two events: polio vaccination in Pakistan after a news story about a Central Intelligence Agency vaccination ruse and subsequent attacks on health care workers, and a controversial episode in a television program about adverse events following human papillomavirus vaccination. For both events, increased online activity was detected and characterized. For the first event, Twitter response to the attacks on health care workers decreased drastically after the first attack, in contrast to mainstream media coverage. For the second event, the mainstream and social media response was largely positive about the HPV vaccine, but antivaccine conversations persisted longer than the provaccine reaction. Using the Vaccine Sentimeter could enable public health professionals to detect increased online activity or sudden shifts in sentiment that could affect vaccination uptake.**

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John S. Brownstein is cofounder of and a senior executive adviser at Epidemico and chief innovation officer at Boston Children's Hospital, in Massachusetts.

Effective monitoring of public conversations and attitudes about vaccination is essential for public health professionals and policy makers to better understand and address vaccine hesitancy.[1,2] Vast and varied conversations on vaccination are going on globally in both mainstream media and social media. Routinely listening to this discussion and tracking current topics, sentiment, questions, and issues could help immunization program officers better understand and address public concerns about vaccines; rapidly identify, analyze, and respond to emerging controversies related to vaccines; and measure the public's reaction to vaccination campaigns.

Previously, the Vaccine Confidence Project used media surveillance to classify, quantify, and analyze public concerns around vaccines.[3] Additionally, there are a growing number of commercial services for general social media monitoring (such as Crimson Hexagon and ExactTarget), as well as free tools for simple social media searches (such as Klout, TweetDeck, and Google Alerts). However, all of these tools are either proprietary or not tailored to a public health context.

We developed a prototype of an open-access

system for monitoring vaccination-related content in both mainstream and social media, called the Vaccine Sentimeter.[4] This is a work in progress, with robust validation yet to be completed. In this article we describe the system, its current operability, and how it was used to follow and analyze two vaccination-related events.

Study Data And Methods

DATA COLLECTION The Vaccine Sentimeter is a web-based system developed by the authors at Epidemico, ProMED-mail, and Sanofi Pasteur, based upon our earlier collaboration with Boston Children's Hospital and the London School of Hygiene and Tropical Medicine.[3] The system provides real-time surveillance of vaccination conversations from mainstream and social media using technology described elsewhere.[5,6]

Mainstream media articles are collected from over 100,000 online sources, including online news sites, blogs, expert-curated discussions, and validated official reports. The sources are searched every hour using vaccine-specific search taxonomy in English, Spanish, and French through the HealthMap system, which provides disease outbreak monitoring and real-time surveillance of emerging public health threats from informal online sources.[5,6] The taxonomy includes generic and brand names of vaccines, vaccine-preventable disease terms, ingredient names, colloquial terms referring to vaccines, and exclusion terms for animal vaccines.

Data collection for the Vaccine Sentimeter began in May 2012. Although data are continuously being collected, they have not been processed and visualized on the system beyond November 2014 because of budget constraints.

Social media posts are collected through the publicly available Twitter Application Program Interface, using vaccine-specific taxonomy in English. The collection began in October 2012. Data processing ended in November 2014, although data collection and storage are ongoing.

DATA PROCESSING Vaccine-related media reports and tweets were automatically and manually processed using HealthMap technology.[5,6] Automatic processing entailed tagging with date, source, vaccine type, and location (if available). Automated tagging was followed by human curation of each article or tweet to validate and correct (if needed) the automated tags and to assign a sentiment to the article or tweet (positive, neutral or unclear, or negative). For example, negative sentiment was assigned if the curator determined that the article or tweet would lead a reader to be less inclined toward vaccination. Positive sentiment was assigned to articles and tweets that communicated public health benefits of vaccination or encouraged vaccination. Neutral or unclear sentiment was assigned to reports about research findings or a person's statement that he or she had been vaccinated without any associated sentiment. The curation protocol has been discussed in detail elsewhere.[3]

DATA ANALYSIS During the collection and processing of Vaccine Sentimeter data, curators detected an increase in the volume of conversation about many vaccine-related events. We selected two of these events, which are analyzed in this article.

The first event was the July 11, 2011, publication of a story in the *Guardian*, a British national daily newspaper, about a fake vaccination campaign orchestrated by the US Central Intelligence Agency (CIA) in Pakistan.[7] According to the article, the intent of the CIA operation was to obtain DNA samples from Osama Bin Laden's family members to confirm his presence before the United States launched a risky operation to apprehend him. After the ruse was revealed, violence against health workers in Pakistan increased, as did the number of polio cases.[8]

To analyze this event, mainstream articles tagged with the vaccine type of polio and the location of Pakistan were used. We used data from May 2012 to May 2014, the date around which we began this analysis. Tweets from October 2012 to May 2014 with a vaccine type matching polio or vaccination in general and tweets containing the terms *Taliban* or *Pakistan* were used. A sample of the resulting data set was manually examined and confirmed to be relevant to the case.

The data set for analysis consisted of 5,964 relevant mainstream media reports and 39,308 relevant tweets. Because of the large number of tweets in this case, they were not curated for sentiment. Mainstream news articles were, but we looked only at volume over time in this case, to allow comparison with the Twitter activity.

The second event that we analyzed was a December 4, 2013, segment on an episode of *Katie*, the US television personality Katie Couric's show on the ABC network. During the segment, titled "HPV Vaccine Controversy," two mothers claimed that their daughters had suffered adverse events following vaccination for human papillomavirus (HPV). One of the daughters died.

The show quickly became controversial, as viewers and others expressed dissatisfaction with its perceived antivaccine bias. A week later Couric released a written response acknowledging that some of the criticism "was valid" and that the segment "spent too much time on the serious adverse events that have been reported in

We hope this tool will help shape a culture of listening and public engagement among public health professionals.

very rare cases following the vaccine. More emphasis should have been given to the safety and efficacy of the HPV vaccines."[9]

For this event, mainstream articles from November 2013 to January 2014 tagged with vaccine type HPV and including the name *Couric* in the headline were selected. The 160 articles were curated for sentiment. The date range ended two months after the event to measure the immediate reaction to it. Tweets tagged with vaccine type HPV or general vaccination and including the name *Couric* in the content were selected and curated for sentiment; there were 1,534 tweets. *Katie* was not used as a search term because of noise associated with common first names. A sample of this data set was manually examined and confirmed to be relevant to the case.

For general HPV sentiment (whether or not specifically referencing this event), 1,883 mainstream news articles and 16,781 tweets from August 2013 to July 2014 tagged with vaccine type HPV were analyzed to observe sentiment during a one-year period. All of the mainstream news articles and a random sample of 3,595 tweets were tagged for sentiment.

LIMITATIONS Our study had a number of limitations. The Vaccine Sentimeter's data sources are not exhaustive and are limited to publicly available data. Additional social media data sources beyond Twitter (such as Instagram, YouTube, and Snapchat) could be added, and the categorization of mainstream versus social media could be further delineated. In addition, using a larger data set curated for sentiment would have permitted a more robust analysis.

Furthermore, although efforts were made to maintain consistency between curators (such as protocol development and interrater verification during early stages), human curation of sentiment is by nature subjective. Lastly, this analysis probed only the first relevant outcome of exposure to media: public sentiment. We intend to conduct future studies to analyze downstream health outcomes, such as vaccine coverage or disease incidence.

Study Results

USING THE VACCINE SENTIMETER Automatically and manually processed data are visualized in the Vaccine Sentimeter in an interactive and searchable way. Mainstream articles are displayed geographically by percentage of negative sentiment in each country, and a list view shows date, article title, vaccine, category, sentiment, and location. Data can be filtered by specific vaccines, locations, categories, and date ranges. For tweets, temporal volume and sentiment trends are shown by vaccine type. Searches can be saved, and results can be exported for further analysis.

The Vaccine Sentimeter dashboard is open access and available online with a user's manual.[4] It can be used to detect early signals in shifting conversations about vaccination and to conduct case studies such as the ones we describe below. At the time of publication, the system shows data from 2012 to 2014.

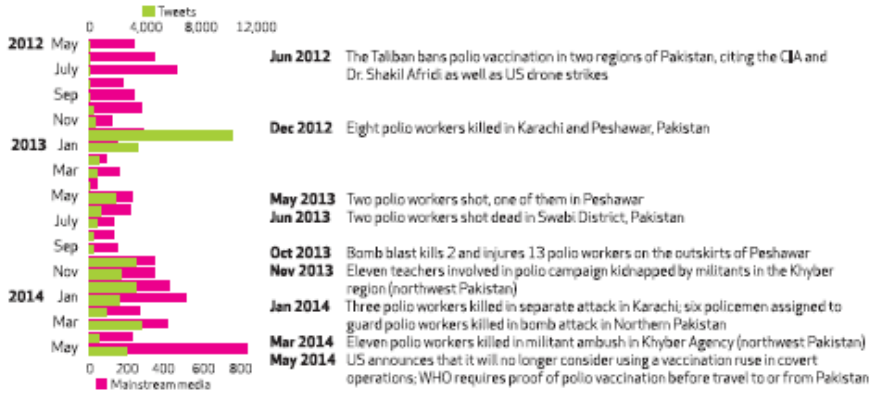
THE PAKISTAN VACCINATION RUSE Analysis of Vaccine Sentimeter data identified clear spikes of activity around high-profile events—both violent and nonviolent—related to the CIA vaccination ruse in Pakistan (Exhibit 1). Twitter activity differed somewhat from activity in the mainstream media. The first spike in mainstream media activity (a 50 percent increase in articles) was observed in June 2012, when the Taliban announced a ban on polio vaccination campaigns in response to US drone strikes.[10] This came at a time when the Global Polio Eradication Initiative had been making progress: Only twenty-two new cases of polio were reported in Pakistan during January–June 2012, compared to fifty-two new cases during the same period in 2011.[11]

The first and largest spike in Twitter activity occurred in December 2012 (Exhibit 1). The 10,442 tweets recorded that month represented a 26.6-fold rise compared with tweets in the previous month. This increase coincided with the deadly December attack on polio workers, the first in a series of violent acts carried out by the Taliban against vaccination workers. For the six attacks that followed the one in December 2012, Twitter volume ranged from 8.1 percent to 36.9 percent of that observed after the first attack—or from 837 tweets in June 2013 to 3,856 in March 2014.

Mainstream media activity was more consistent than Twitter activity following these violent events. In December 2012 there were 284 related articles in the mainstream media, and in subsequent months with violent events, the volume

EXHIBIT 1

Mainstream Articles And Tweets About Polio Vaccine In Pakistan Per Month, May 2012–May 2014



SOURCE Vaccine Sentimeter (Note 4 in text). **NOTES** Twitter data for May–September 2012 were unavailable. CIA is Central Intelligence Agency. WHO is World Health Organization.

ranged from 209 to 508 articles (63–154 percent of the average of 330 articles per month). January 2014, in which two violent events involving polio vaccination occurred in Pakistan, saw the most articles (508) of these months.

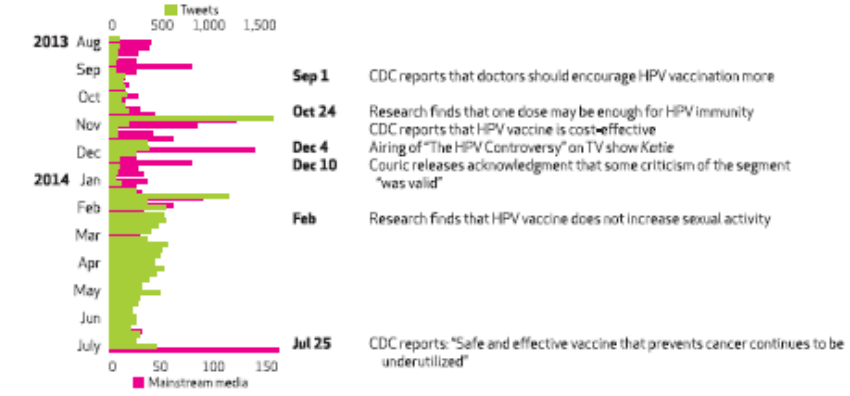
'HPV VACCINE CONTROVERSY' TELEVISION SEGMENT Following the airing of the *Katie* show's segment "HPV Vaccine Controversy" on December 4, 2013, an increase in HPV vaccine–related conversations was observed in the Vaccine Sentimeter system, in both mainstream media and Twitter (Exhibit 2).

Specifically in reference to the episode, sentiment toward the HPV vaccine was overwhelmingly positive in the mainstream media (95.8 percent of articles) (Exhibit 3). Twitter content was also quite positive about the HPV vaccine (77.5 percent of tweets) from the day before the episode aired (when previews of it were released) to ten days after the airing, but 78.6 percent of tweets from December 15 to January 31 were negative (Exhibit 4).

However, the *Katie* episode did not have a lasting impact on overall sentiment toward the HPV

EXHIBIT 2

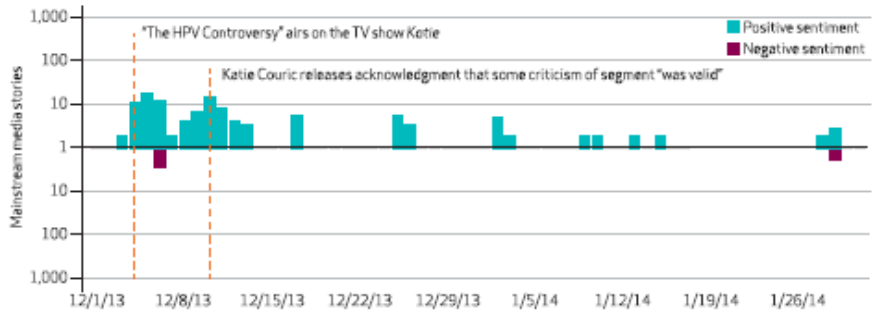
Mainstream Articles And Tweets About Human Papillomavirus (HPV) Vaccine Per Week, August 2013–July 2014



SOURCE Vaccine Sentimeter (Note 4 in text). **NOTE** CDC is Centers for Disease Control and Prevention.

EXHIBIT 3

Volume And Sentiment Of Mainstream Media Activity Referencing Broadcast Of "HPV Vaccine Controversy" Segment, Per Day, December 2013–January 2014



SOURCE Vaccine Sentimeter (Note 4 in text). **NOTE** The *y* axis uses a log scale.

vaccine (for additional data on overall sentiment, see the online Appendix).[12] In the mainstream media, positive sentiment prevailed before and after the event (over a one-year period, the weekly average was 75.5 percent positive; for the data, see Appendix Exhibit 1).[12] On Twitter, the predominant sentiment toward the HPV vaccine before the event was negative, and although there was a decrease in negative sentiment when the episode aired, the sentiment had returned to baseline levels two weeks after its airing (over a one-year period, the weekly average was 74.9 percent negative; for the data, see Appendix Exhibit 2).[12]

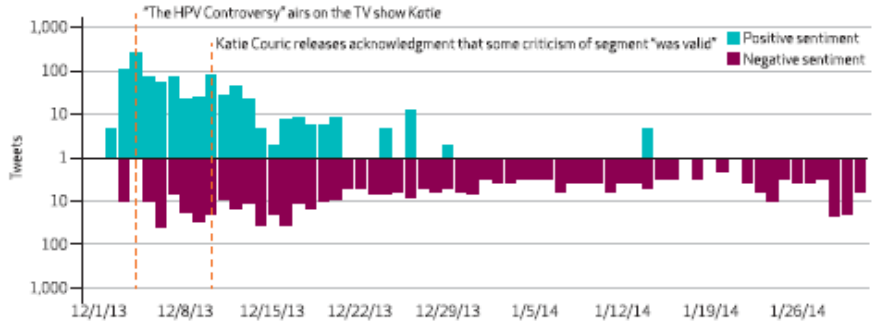
Discussion

We have illustrated how the Vaccine Sentimeter can be used to monitor vaccine-related conversations online. This system enables public health professionals to detect signals that may affect vaccination uptake, such as increased online activity or sudden shifts in sentiment following vaccination-related events.[13] Access to mainstream and social media conversations during such events can help health authorities anticipate, understand, and respond to the public's questions and concerns. Media scholar John M. Culkin once said, "We shape our tools, and thereafter our tools shape us."[14] We hope this tool will help shape a culture of listening and public engagement among public health professionals.

Analysis of two events revealed different

EXHIBIT 4

Volume And Sentiment Of Tweets Referencing Broadcast Of "HPV Vaccine Controversy" Segment, Per Day, December 2013–January 2014



SOURCE Vaccine Sentimeter (Note 4 in text). **NOTE** The *y* axis uses a log scale.

trends in the mainstream and social media. In the polio vaccine case, Twitter reaction to the first attack targeting health care workers was markedly elevated compared to reactions to subsequent violence, whereas mainstream media coverage was more consistent in volume over time. This may suggest that interest in a topic is more likely to wane on Twitter than in the mainstream media, but further research is needed to support that conclusion.

The HPV vaccine case showed that the antivaccine conversation lasted much longer than the provaccine reaction. This is in line with well-established psychosocial theories that describe the disseminative nature of misinformation or rumors and the difficulty in correcting them—especially when the misinformation fits with existing beliefs.[15–17]

Further, a look at the baseline sentiment toward HPV vaccine (not specific to this case) showed that sentiment in the mainstream media was predominantly positive toward vaccination, while on Twitter the predominant sentiment was negative. The Vaccine Sentimeter may help vaccination program officers understand in real time which topics or issues need to be addressed in which channels, thus facilitating a tailored and responsive public engagement strategy.

As the two cases exemplify, the Vaccine Sentimeter can serve as a real-time monitoring tool for public health organizations and professionals worldwide to keep abreast of local conversations about vaccination and identify geographic or topical trends in misinformation. For example, a staff member of a state health department might perform a weekly review of local activity to identify any rumors about vaccines or to scan for reactions to a local vaccination campaign. This information could then inform a press release, a subsequent vaccination campaign, or a direct response to online content.

We recognize that such data-based "listening" is the first of many steps in addressing vaccine hesitancy and leading to behavior change. But to our knowledge, before the Vaccine Sentimeter there was no alternative open-source tool for this crucial starting point. There are commercial services for general social media analysis, but they require paid subscriptions, involve extensive user set-up processes (such as Boolean search queries or visualization widgets), and are often limited to automated processing. Existing free online tools for exploring social media have very limited features. The Vaccine Sentimeter enhances these raw social media data feeds through automated and manual processing specific to vaccine hesitancy.

We recognize that data-based "listening" is the first of many steps in addressing vaccine hesitancy and leading to behavior change.

The Vaccine Sentimeter is a prototype and a work in progress. To validate it and build it into a predictive tool, we envision that the next phase of the project will include additionally overlaying downstream outcomes of nonvaccination, such as incidence of vaccine-preventable disease. Furthermore, data sources could be differentially weighed by credibility, reach, or both, and other data sources could be added. Finally, automated processing could be improved to minimize manual involvement—for example, by using machine learning to train sentiment tagging—thereby increasing the relative value of insight output to resource input.

Conclusion

The automated collection and analysis of vaccine-related media reports and social media posts by systems such as the Vaccine Sentimeter enable the visualization and monitoring of vaccination-related conversations in real time. In addition to mainstream sources, the system accesses blogs and online communities that might not otherwise be on the radar of public health professionals. The Vaccine Sentimeter is freely available online,[4] and we envision the possible adoption of this practical tool by program managers, policy makers, and health care providers around the world. We further hope that this tool will help shape a culture of listening, understanding, and public engagement among public health professionals. ■

The data collection and research were partially funded by Sanofi Pasteur. Epidemico Inc. is a company attempting to commercialize the information technology aspects of this research. The authors thank Susan Aman and Harold Rodriguez for their work on the software development of the Vaccine Sentimeter, Elizabeth Traphagen for assistance on data curation, and Julia Lien for the graphics submitted with the manuscript for this article.

NOTES

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12 To access the Appendix, click on the Appendix link in the box to the right of the article online.

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ANNEX 4. What the public wants to know about human papillomavirus vaccines: global media monitoring and coverage analysis using a 'virtual questions' approach [draft]

What the public wants to know about human papillomavirus vaccines: global media monitoring and coverage analysis using a 'virtual questions' approach

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on behalf of the ADVANCE consortium

Word count: 3167

Abstract
The benefit-risk balance of vaccines is regularly debated by the public and in the media, but the utility of medicinal product-specific media monitoring for regulatory bodies is yet unclear. A pilot was therefore conducted at the European Medicines Agency (EMA) with regard to human papillomavirus (HPV) vaccines from September to December 2015 to support a European Union (EU) referral procedure assessing potential causality of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS), both reported to the authorities as suspected adverse reactions.
Objectives: The pilot was conducted to support the EMA and test the utility of media monitoring in real life. The outcome should also inform communication strategies as part of vaccine benefit-risk monitoring methods under development by the IMI-ADVANCE project.
Methods: Daily media monitoring of worldwide online news in most EU languages and analyses of topics, concerns and information gaps with translation into 'virtual questions' and subsequent evaluation of utility.
Results: About 60-100 news items were identified daily and analyses performed weekly. The news items presented personal stories and over time increasingly included scientific and policy/process-related points. Explicit and implicit questions were identified as well as issues which might not have been discussed if the discussant would have had more information. These were formulated as 50 'virtual questions' in 12 areas. At the EMA, this helped covering public concerns and information needs regarding CRPS and POTS by the assessment, impacted on the content and tone of public statements, and predicted all questions raised by journalists at the press briefing. It further helped the EU Member States' authorities in understanding their national communication demands in the global context.
Conclusions: The pilot demonstrated potential utility of media monitoring for regulatory bodies in their efforts to support trusted, safe and effective use of vaccines. As a next step, focus should be on developing efficient monitoring strategies. This pilot suggests that efficient media monitoring strategies could be part of a regulatory surveillance for medicinal products of high public health impact and/or high public interest.

Keywords: Vaccines, HPV vaccines, media, media coverage, media monitoring, communication, regulatory authorities, EMA

INTRODUCTION

The benefit-risk balance of vaccines is a topic regularly debated in the public domain and in particular in the media. These debates are linked on one hand to the high expectations people have towards vaccines as one of the most successful health interventions to date [1] and on the other hand to the phenomenon of vaccine hesitancy [2]. Media attention increases every time when there is information on a new vaccine or a new safety concern. Regulatory bodies may be put in the spotlight, as they are in charge of vaccines licensure and surveillance of their safety and efficacy and, if needed, of taking risk minimising or other action. They also need to inform the public about the outcome of their assessments and provide advice on safe and effective use of vaccines [3].

As communication starts with listening, regulators need to find ways to listen to the public. This should also ensure that concerns expressed by the public are addressed in risk assessments [4], so that information, based on evidence and plausibility as well as on honesty over uncertainty, can be provided to the public. Furthermore, listening provides an opportunity to gather data contributing to a body of evidence or its interpretation, including data on the real world use of medicines. Listening is also a fundamental element of a proposed new vaccine communication model which envisions communication as integrating safety assessment and trust-building strategies [5].

Listening mechanisms available to regulatory bodies include direct interaction with members and representatives of the public (e.g. through working groups, public hearings, information contact points), conducting or reviewing research (e.g. surveys), as well as media monitoring. The utility of medicinal product-specific media monitoring for regulatory authorities is however yet unclear.

OBJECTIVE

The aim of this article is to report and discuss the results of a prospective pilot study, evaluating the role of media monitoring in vaccine communication. Debates about vaccines in the media have some aspects in common to all vaccines, but there are also sentiments expressed specific to certain vaccines [6], which may drive the media debate. The pilot study was initiated in September 2015 when a European Union (EU) referral procedure for human papilloma virus (HPV) vaccines was ongoing for the assessment of potential causality of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS), both reported to the authorities as suspected adverse reactions [7].

The specific objective of the pilot was to learn from the online news media and blog posts what topics, concerns and questions in relation to HPV vaccines were discussed in the public domain and how a media coverage analysis could inform the communication preparations at the EMA.

This pilot was conducted as a deliverable for the Accelerated Development of VAccine benefit-risk Collaboration in Europe (ADVANCE), a private-public consortium aiming to establish a reliable, valid and tested framework providing rapidly robust data and scientific evidence on vaccine benefits and risks in Europe. As part of this project, ADVANCE is developing best practice guidance including recommendations for communications on vaccines safety [8].

It is *not* the objective of this article to provide information on the safety profile of HPV vaccines or to explain the outcomes of the EU referral procedure on HPV vaccines and CRPS/POTS, as these outcomes are presented elsewhere [7, 9].

METHODS

Search strategy

Using the Cision® media monitoring system, all online new stories and blog posts available in the system from any country in the world were screened, including coverage from the following media types: health, science, news and tabloid media, regional websites, online sites of television channels and blogs. As it was considered possible that some relevant news would only be picked up in media with small reach or blogs, no restriction was applied (e.g. by media type, size of readership and size of country of origin).

The time period of the monitoring lasted from 7 September to 23 December 2015, i.e. starting about two months before the meeting of the EMA Pharmacovigilance Risk Assessment Committee (PRAC), for which the conclusion of their HPV vaccines assessment for the referral procedure was scheduled, and ending three weeks after the publication of the PRAC outcome by the EMA.

The following colloquial and technical search terms were defined for the screening: "HPV vaccin*"; "papilloma W/3 vaccin*"; "cervical cancer vaccin*"; "HPV jab"; "Gardasil"; "Cervarix"; "Silgard". The asterisk symbol (*) indicates that the ending of 'vaccin' could vary (e.g. vaccin*e*, vaccin*ation*). 'W/3' (or W/2, W/4, W/5 etc.) indicates the number of words which could be inserted between two word elements of a search term. The search terms were translated into all official EU languages (with the exception of Irish and Maltese) by native speakers at the EMA.

Daily media screening
The media monitoring was carried out daily by JF. Due to the application of the search terms in 22 languages without any exclusion criteria, the system picked up a large number of news stories and blog posts. Irrelevant ones were deleted from the media monitoring database, e.g. those about business and financial news not including any information relevant to the objective of the pilot). For articles in languages other than English, Google Translate® was used for initial understanding and the critical news stories were accurately summarised by native speakers at the EMA. No specific coding was used to categorise the articles, as the aim was to conduct a content review for identifying the topics of interest and subsequently formulating considerations for communication preparations.

Weekly analysis of media coverage and reporting
A short summary of the media coverage with key topics and charts by date and by country were compiled for weekly media monitoring reports, which also contained key considerations for communication preparations formulated on the basis of a content review of the coverage. The key considerations reflected upon concerns, information needs and expectations of the public in relation to HPV vaccines and their assessment by regulatory authorities.

Formulating 'virtual questions'
A cumulative review of the weekly analyses and key considerations was performed in the month prior to finalisation of the PRAC assessment with the aim to prepare for the communication of the outcome. This aimed at understanding questions and concerns raised in the media explicitly or implicitly, including those raised due to lack of information and those that could be anticipated once more information would be provided. Blogs in which healthcare providers shared what they are frequently asked by parents and how they respond were also reviewed. All identified questions and concerns were translated by PB into 'virtual questions', i.e. questions derived from media monitoring which were considered as important for regulatory authorities to communicate proactively or be prepared to answer. The virtual questions were formulated with terms commonly used in the regulatory and scientific environment.

Evaluation of utility
In order to evaluate the utility of medicinal product-specific media monitoring for regulatory authorities, the following was undertaken: (1) obtaining feedback from colleagues using the media monitoring results; (2) reviewing how the assessment was presented in the summary of PRAC recommendations with a view on how the virtual questions were addressed; and (3) comparison of questions raised by journalists with the virtual questions to evaluate their predictive capacity.

RESULTS

Media coverage
A total of 4230 "news clips", i.e. news stories and blog posts (493), were collected during the whole monitoring period (after deletion of irrelevant coverage in the Cision® system). The highest media coverage for Europe in terms of absolute numbers of articles (Figure 1) was found in Denmark, while worldwide the biggest number occurred in the United States (> 1000). Analysis of intensity of coverage for HPV vaccines by day from 7 September to 23 December 2015 (Figure 2) identified six peeks in time related to triggering events (Table 1).

Figure 1. Map depicting volume of media coverage from 7 September to 23 December 2015 by European country (generated by the Cision® media monitoring system on the basis of origin country of the news source as provided by the country metadata on the given website)

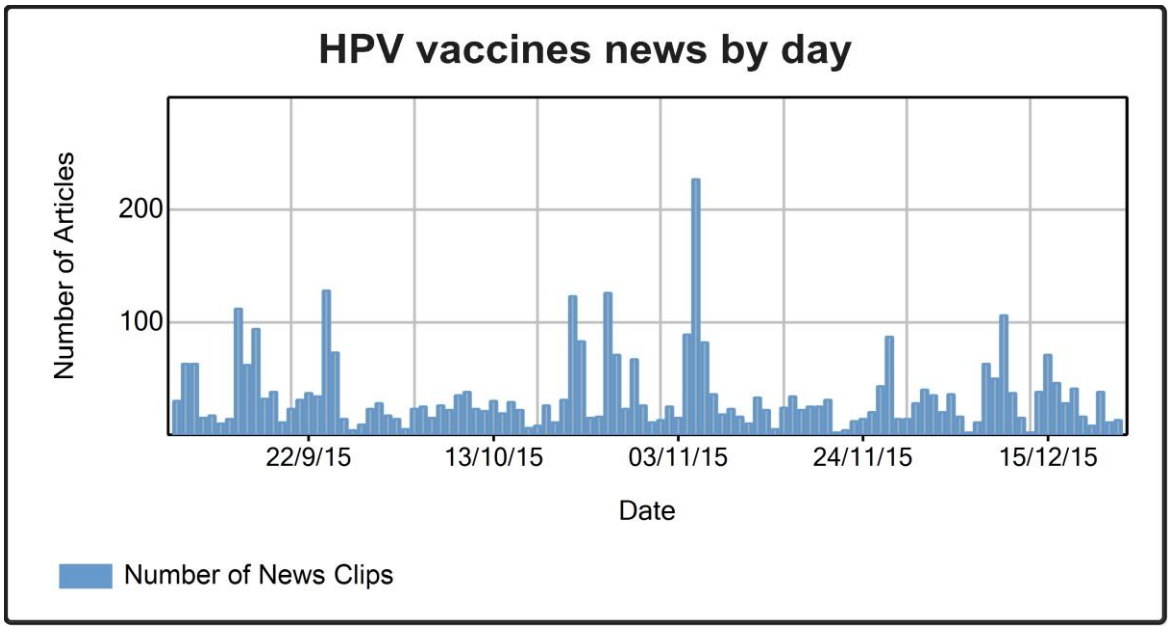

Figure 2. Time chart depicting volume of media coverage worldwide from 7 September to 23 December 2015 by day (generated by the Cision® media monitoring system)

Table 1. Peeks of the media coverage on HPV vaccines worldwide from 7 September to 23 December 2015

Peek time	Peek-triggering event
1st peek, 14 September 2015	Study published by the French National Agency for Medicines and Health Products Safety (ANSM – Agence Nationale de Sécurité du Médicament et des Produits de Santé) and the French health insurance, concluding that HPV vaccines do not increase the risk of auto-immune disorders but suggesting increase of the risk of Guillain-Barré syndrome [10]
	Call by two Republican Party lawmakers in the United States towards schools to oppose mandatory HPV vaccination of middle school students in Rhode Island [11]

2nd peek, 24 September 2015	Statement of the Catholic bishop in British Columbia, Canada saying abstinence is the only healthy choice over HPV vaccination [12]
	Announcement in Denmark of the replacement of Gardasil by Cervarix in the national HPV immunization programme [13]
	Report claiming that 1500 girls in Denmark have suspected adverse reactions to HPV vaccines [14]
3rd peek, 22 October 2015	Study published in Epidemiology, Biomarkers and Prevention concluding that a quarter of doctors in the United States do not strongly endorse HPV vaccination [15]
4th peek, 26 October 2015	Statement of the International Papillomavirus Society (IPVS) endorsing the use of HPV vaccines [16]
	Concerns in Denmark on the marketing authorisations holder's restrictive search strategy on the side effects of HPV vaccine [17]
	Study published by the US Centers for Disease Control and Prevention (CDC) about low HPV vaccine uptake among adolescent males in the United States [18]
5th peek, 5 November 2015	Publication by the EMA of PRAC outcome of the referral procedure, concluding that the evidence does not support a causal association between HPV vaccines and CRPS or POTS [19]
6th peek, 10 December 2015	Statement by Health Canada referring to a review of international research data suggesting that there are no new risks associated with Gardasil and that it can be used safely [20]

Table 2. shows the topics mostly discussed during the monitoring period in terms of the volume of media coverage or the relevance of the issue as considered by the reviewers**.**

Table 2. Key topics subject to media coverage for HPV vaccines worldwide from 7 September to 23 December 2015[1]

Key topics
Experiences of female adolescents with suspected adverse reactions of HPV vaccines and beliefs in causal association with HPV vaccines [21]
Number of suspected adverse reaction reports received in Denmark [14], and concerns in Denmark on the marketing authorisation holder's restrictive search strategy on the side effects of HPV vaccine [17]
Statements from parents claiming they were not sufficiently informed about the adverse reaction profile of HPV vaccines before their decision-making on vaccination [22, 23, 24]
Questions about safety and benefits of HPV vaccines [25, 26]
Study on misleading information on HPV vaccines on the internet [27]
Lack of treatment options for CRPS and POTS [28]
Activities of anti-HPV vaccination groups and opinion leaders [12, 29, 30, 31, 32, 33, 34]
Protest by parents and activities by politicians against mandatory HPV vaccination in Rhode Island, United States [11, 35]
Call by the Irish government for investigations on suspected adverse reactions with HPV vaccines [23]
Suspended HPV vaccination recommendation by the Ministry of Health in Japan [36]
United States presidential candidate Donald Trump claiming a causal association between vaccines and autism [37]
Replacement of Gardasil by Cervarix in the national HPV immunization programme in Denmark [13]
Support to HPV immunization programmes [16, 38, 39, 40]
Reassuring safety and/or benefit data supporting HPV vaccination policies [41, 10, 20, 42, 16]
Protection against genital warts by HPV vaccination [43] [44]
Mouth cancer and the importance of HPV vaccination for boys [45]
Low HPV vaccine uptake by female and male adolescents in the United States [46, 18]
Responsibility of physicians for low vaccination rates [15]
Discussion about appropriate HPV-vaccination age [47]
Mainly neutral, but also some negative media coverage of the PRAC recommendation on referral procedure [4], in particular in Denmark and Sweden [48, 49]
Need for further independent studies on the association between HPV vaccines and CRPS/POTS [50, 51, 52]

Virtual questions

[1] The references do not show all news stories/blog posts but the key source as far as identifiable or selected examples.

50 virtual questions were formulated, which could be grouped into 12 areas with a principle question each and sub-questions on specific aspects (see Table 3).

Table 3. Virtual questions formulated on the basis of a content review of the media monitoring results for HPV vaccines worldwide 7 September – 22 October 2015

Principle question	Additional sub-questions
Question area 1 on assessment scope: **1.0.** What is the scope of the assessment conducted for the EU referral procedure for HPV vaccines?	**1.1.** Why does the procedure focus on CRPS and POTS as defined by complex and difficult to apply/ascertain case definitions ?
	1.2. Why have concerns over autoimmune diseases with HPV vaccines been excluded from the assessment?
	1.3. Why does the evaluation not cover the entire benefit-risk balance of HPV vaccines?
Question area 2 on CRPS and POTS case data: **2.0.** What kind of case reports of CRPS and POTS in association with HPV vaccines have been reviewed by the competent authorities, and how?	**2.1.** How many case reports of CRPS and POTS in association with HPV vaccines have been received by the competent authorities, who reported the cases to the competent authorities and who are the primary reporters?
	2.2. Who confirmed the cases as CRPS and POTS cases?
	2.3. How many cases have been received with symptoms of or similar to CRPS and POTS but have not met the criteria of the case definitions, how were these cases reviewed/followed up and how did they impact on the assessment outcome?
	2.4. Have all reported cases been followed up by the competent authorities in order to obtain more information (to allow for causality assessment)?
	2.5. What is the outcome of the analysis of data recorded in EudraVigilance (the adverse reaction database of the EU regulatory network) requested by parents who have participated in the EMA meeting with concerned vaccinees and parents to present their concerns and experiences?
	2.6. How were the cases reviewed that had been submitted to the competent authorities by the parents' groups as invited by the EMA?
Question area 3 on frequency assessment: **3.0.** What are the reporting rates and actual frequencies of CRPS and POTS in association with HPV vaccines?	**3.1.** How are these frequencies calculated?
	3.2. Where have background frequency data been obtained from and how confident can one be in their accuracy?
	3.3. What is the likely magnitude of underreporting and has a sensitivity analysis been performed for the observed/expected analysis to take underreporting into account?
	3.4. Why are the reporting rates for (any) adverse reactions higher for HPV vaccine than for other vaccines?
Question area 4 on other (i.e. not case) CRPS and POTS data: **4.0.** What kind of data has been reviewed for the EU referral procedure for HPV vaccines in addition to individual case reports?	**4.1.** What is the nature of these data, and who provided them?
Question area 5 on assessment of causal association: **5.0.** How has the assessment of CRPS and POTS in causal association with HPV vaccines been performed?	**5.1.** Have all potential aetiological pathways been investigated, e.g. autoimmune pathway and impact of female hormones on susceptibility for autoimmune disease?
	5.2. How has causal association been ruled out?
Question area 6 on overall safety and other safety concerns: **6.0.** What are the overall safety database and safety study results for HPV vaccines?	**6.1.** What was the knowledge base at the time of granting the marketing authorisation and were the vaccines sufficiently tested at the time?

	6.2. How are data assessed for autoimmune diseases, including for multiple sclerosis and Guillain-Barré syndrome?
	6.3. How are data assessed for infertility, miscarriage and stillbirth?
Question area 7 on aluminium: **7.0.** What is the knowledge about the safety of aluminium/AS04 as adjuvant?	**7.1.** What are the plasma levels for aluminium after vaccination with current HPV vaccines and with the future GARDASIL-9 compared to typical food intake?
	7.2. How does the clearance process of aluminium in the human body work?
	7.3. Since when has the rate of autism diagnosis been increasing and is there a temporal association with the use of aluminium in vaccines?
	7.4. What is known about a link between AS04 (aluminium hydroxide + monophosphoryl lipid A) and autism?
	7.5. How similar is AS04 to AS03 (squalene+ DL-α-tocopherol+polysorbate 80), which is the adjuvant in PANDEMRIX for which cases of narcolepsy were reported as suspected adverse reactions?
Question area 8 on data trustworthiness: **8.0.** Are the data for the EU referral procedure for HPV vaccines trustworthy?	**8.1.** What safeguards are there that marketing authorisation holders do not manipulate data they submit to competent authorities?
	8.2. Have data been solicited by competent authorities from independent sources?
Question area 9 on assessment standards and integrity: **9.0.** How can it be demonstrated that signal detection, risk evaluation and decision-making have been performed to highest standards during the EU referral procedure for HPV vaccines?	**9.1.** Have competent authorities taken seriously the vaccinated females experiencing CRPS and POTS?
	9.2. How do competent authorities manage their conflict of interests?
	9.3. Why was the signal of CRPS and POTS with HPV vaccines not identified earlier, and why was the referral procedure only initiated at the request of Denmark and not earlier by the EMA?
	9.4. Why did the EMA not apply the precautionary principle and suspended the vaccine while investigations were ongoing?
Question area 10 on benefit: **10.0.** What is the knowledge on the benefit and effectiveness of HPV vaccines?	**10.1.** How does the vaccine intervene protectively in the pathway of cancer development?
	10.2. How long is the vaccination effective in vaccinees, and what should vaccinees do after immunity has decreased?
	10.3. What is the potential of strain replacement and how will this impact on cancer rates?
Question area 11 on benefit-risk balance: **11.0.** What does the statement 'the benefits outweigh the risks' mean?	**11.1.** Is this statement only applicable at population level, or also at individual level, and does a positive benefit-risk balance apply to all potential vaccines or are there individuals to whom the statement does not apply?
	11.2. How are healthcare professionals be provided with information so that they can communicate well with potential vaccinees and parents about the individual benefit-risk balance?
Question area 12 on further steps and research: **12.0.** What will the impact of the referral outcome be and will further research be done?	**12.1.** How do vaccine evaluations by competent authorities impact on immunization policies?
	12.2. What kind of further research will be done and what will be the study objectives?
	12.3. How will independence of this research be assured?

Observations regarding public expectations

The content review of the media coverage also identified patterns: While many debates remained nationally contained, some news travelled, in particular between Scandinavian countries and those countries with active parents' groups, such as Demark, Ireland and the United Kingdom. There was also a change in the public debate over time. In particular, in Denmark the debate moved from presenting personal stories to additionally including scientific and policy-related points. There were increasingly references to scientific publications on safety aspects, and overall the debate turned from questioning vaccine safety as such to doubting the trustworthiness of the data, pharmaceutical industry as a data source and the integrity of the regulators. This shows the importance of preparing for communication given its complex relationship with transparency and trust. In particular, this led to including in the key considerations that regulatory authorities should be prepared to answer in detail how they assure the legally demanded independence of their work and how the pharmaceutical industry is inspected for compliance with the legal requirements.

The content review further allowed better understanding of some of the motivations and expectations of parents. Parents in general consider the information they receive on vaccine risks as being insufficient. Parents who suspected that their daughters had been harmed by HPV vaccination mainly wanted to provide case information to the authorities, obtain "support" and treatment within the governmental health insurance as well as remedy "the lack of respect" for their daughters. Some also requested ending the HPV vaccination programme or wanted other parents to be provided with information about the ongoing EMA referral review, so that they can give an "informed consent" to vaccination. Giving special attention to respectfully acknowledge the health status of the patients, regardless of what the outcome of the referral would be, was therefore added to the key considerations for preparing communication.

Utility

The utility of medicinal product-specific media monitoring for regulatory authorities manifested itself at three levels: the EMA communications department, PRAC and the Member States. The media monitoring helped the EMA media office to be prepared if any emerging issues needed immediate attention. The weekly media monitoring reports, the cumulative key considerations and the virtual questions were circulated within the EMA and the PRAC.

(1) Feedback from users of the media monitoring results

Member State representatives stated that the reports helped them to put the media attention at national level in a broader European and global context. They further noted that the weekly key considerations enhanced their communication preparedness for questions from the public they had not thought of before.

A cumulative look at the then available key considerations was taken at PRAC level in early October 2015, and the PRAC members leading the HPV vaccines assessment confirmed that all identified public concerns and information gaps relating to CRPS and POTS would be covered by the ongoing assessment. It was considered that the broader public concerns, such as those regarding aluminium-containing adjuvants, had been evaluated in the context of previous assessments. This provided reassurance that no additional data reviews would be necessary to respond to questions from the public as anticipated.

In October and November 2015, the EMA writers were guided by the virtual questions with regard to which information items from the assessment to include proactively in the summary of PRAC recommendations [19] for publication and dissemination to the EU regulatory network, its international partners, relevant patient and healthcare professional organisations and journalists.

The virtual questions also guided the EMA as to which information to include in the talking points prepared for the EMA itself, as well as for competent authorities in Member States, to enable provision of accurate and consistent information in response to external requests, including those from journalists. The talking points were also used by senior EMA staff members to prepare for attending, upon invitation, the discussion at the Danish parliament in December 2015. The identification of the pattern of the public

debate becoming increasingly focussed scientific and policy-related points was considered to be especially helpful, particularly in Denmark.

(2) Review of impact of the virtual questions on the summary of PRAC recommendations

With regard to the content of the summary of PRAC recommendations, i.e. the public statement on the PRAC outcome [19], the review showed that one question from each question area specific to HPV vaccines and CRPS/POTS, i.e. question areas 1 to 5, was addressed as follows:

- The PRAC "reviewed the published research, data from clinical trials and reports of suspected side effects from patients and healthcare professionals, as well as data supplied by Member States." (addresses virtual questions 2.0. and 4.1.);
- The PRAC "took into account detailed information received from a number of patient groups that also highlighted the impact these syndromes can have on patients and families.…" (addresses virtual question 2.6.);
- "Symptoms of CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals." and "The PRAC noted that some symptoms of CRPS and POTS may overlap with chronic fatigue syndrome (CFS, also known and myalgic encephalomyelitis or ME). Many of the reports considered in the review have features of CFS and some patients had diagnosis of both POTS and CFS. Results of a large published study that showed no link between HPV vaccine and CFS were therefore particularly relevant (addresses virtual question 1.1. and 2.3.);
- "available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year. The review found no evidence that the overall rates of these syndromes in vaccinated girls were different from expected rates in these age groups, even taking into account possible "underreporting" (addresses virtual questions 5.0. and 3.3.).

This review suggested that using the virtual questions formulated on the basis of media monitoring, led to enriching the summary on medical and methodological issues that are contained in the assessment reports made available by the EMA to the public, but usually not in summaries of PRAC recommendations.

With regard to the tone of the summary of PRAC recommendations on HPV vaccines, the review identified words intended to express commitment and diligence towards patients with CRPS and POTS and acknowledged the seriousness of what they were experiencing. The summary highlighted that the scientific review was "detailed", performed "thoroughly" and in consultation with "leading experts". It further stressed that CRPS and POTS "can severely affect the quality of life." This kind of wording is not the routine way of expression of regulatory authorities, which is generally devoid of empathy.

(3) Capacity of virtual questions to predict questions from journalists

At the EMA press briefing [53], four questions were raised by journalists, which were all predicted by the virtual questions and therefore addressed in the talking points, so that EMA staff members could respond immediately. The questions related to the virtual questions areas 2, 3, 4, 5 and 12.

The comparison of the questions sent by journalists to the EMA media office between 1 September to 31 December 2015 demonstrated that medicinal product-specific media monitoring can predict questions from journalists and that talking points addressing the virtual questions can help enable prompt responses. During the referral procedure journalists frequently requested the timetable for finalising the assessment and access to documents or interviews. Twenty journalist enquiries contained actual questions, 12 before and 8 after publication of the PRAC recommendations on 5 November. The questions and comments before corresponded with the virtual questions 1.0, 1.1., 2.0., 2.3. 3.0., 4.0, 5.0., 9.0, 9.2., 10.0., 10.2. and 10.3., and after to 1.1., 2.0., 2.3., 3.0., 3.2., 3.3., 4.0., 7.0., 9.2., 10.0. and 12. 0. In some instances, the level of detail of the questions was however not predicted. At both times, before and after, clarifications on how referral procedures work in general were also frequently

requested. The EMA responded to all questions from journalists, whether or not they were included in the talking points. The EMA's declaration of interest policy and actual experts' declarations are already accessible by the public [54].

DISCUSSION AND CONCLUSIONS

This pilot demonstrated a potential utility of medicinal product-specific media monitoring for regulatory authorities. The potential utility consists of enabling the identification of main concerns and information needs of the public for proactively addressing these in widely disseminated summaries on assessment outcome and for preparing spokespersons for prompt responsiveness to most questions raised by journalists or others.

In order to use resources for media monitoring efficiently, the experience with the pilot suggests limiting the number of languages monitored to English and the languages of those countries with noted high media coverage of the medicinal product. The use of exclusion terms (e.g. budget, profit) to automatically rather than manually exclude e.g. financial news has been discussed as an example, but bears the risk of excluding articles about important policy and trust issues in relation to profit-driven bias suspected by the public and their expectations for independent data gathering and assessment. Further work could go into developing hierarchical or conditional search algorithms to increase the specificity of search strategies without losing sensitivity.

Questions have been raised by vaccine safety experts as to whether listening and providing feedback in response to unsubstantiated concerns voiced by the public could risk spreading concerns further, creating what has been referred to in literature as the "social amplification of risk" [55] While recognising these risks, listening genuinely to public concerns and responding honestly and with transparency is t essential for building and sustaining trust, a fundamental principle in relation to matters of common good.

In conclusion, the following principles and actions are recommended to the IMI-ADVANCE project:

- Efficient media monitoring should be built into the process of vaccine benefit-risk monitoring, and benefit-risk assessment should ensure the provision of responses to all safety concerns, including those debated in the public domain.
- Explanations on methods for benefit-risk monitoring and assessment should be provided in a language understandable to the public, and should be developed and ideally be tested with a view to explaining how the method works, what it can tell us, what its limitations are and how robust the results are.
- Given that conflicts of interests have been identified through the media monitoring as one of the biggest public concerns, the mechanisms of the public-private partnership (PPP) governance model, as envisaged by IMI-ADVANCE, and procedures to ensure unbiased benefit-risk monitoring and assessment need to be actively communicated to the public.

This pilot suggests that efficient media monitoring strategies could be part of a regulatory surveillance for medicinal products of high public health impact and/or high public interest. This could be best progressed in the context of meaningful transparency and trust-building with the public. Overall, medicine safety would benefit from listening to the public and addressing what the different population groups want and need to know for in order to use of medicines safely and effectively.

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