JAHR | Vol. 11/2 | No. 22 | 2020

Review article / Pregledni članak
Received / Zaprimljen: 1. 3. 2020.

DOI: https://doi.org/10.21860/j.11.2.1

Gordana Pelčić*, Salvador Ribas**, Anamarija Gjuran Coha***, Ivana Tucak****, Suzana Vuletić*****, Silvana Pavlinović******, Ana Valković*******

The Place of Big Data in Addressing Emerged Issues in Vaccinology of the 21st Century

SUMMARY

Vaccinology, as a great achievement of public health of the 20th century nowadays faces doubts, questions, and concerns that could be included in the term of vaccine hesitancy. The vaccinology in the 21st century is marked by the emerging anti-vaccine movements followed by a variety of attempts and approaches of professionals to resolve them. The globalization in health care on the one side and great technological achievements, on the other, create the possibilities where an enormous amount of data is publicly available. The professionals have based the benefits of vaccination on scientific data. Vaccine hesitancy and anti-vaccine movements declare that they have also based their policy on scientific data. On the first line

* University of Rijeka, Faculty of Medicine, Department of Social Sciences and Medical Humanities / Health Care Center of Primorsko-Goranska County, Rijeka, Croatia. ORCID ID: https://orcid.org/0000-0002-3322-1470.

** International Society for Clinical Bioethics, Barcelona, Spain. ORCID ID: https://orcid.org/0000-0003-0565-0638.

*** University of Rijeka, Faculty of Medicine, Department of Social Sciences and Medical Humanities, Rijeka, Croatia.

**** Josip Juraj Strossmayer University of Osijek, Faculty of Law, Department of International Public and Private Law, Legal Theory and Methodology, Osijek, Croatia. ORCID ID: https://orcid.org/0000-0001-9694-2315.

***** Josip Juraj Strossmayer University of Osijek, Catholic Faculty of Theology in Đakovo, Department of Moral Theology, Đakovo, Croatia. ORCID ID: https://orcid.org/0000-0002-5629-6635.

****** Hotel Sveti Križ, Čiovo, Croatia. ORCID ID: https://orcid.org/0000-0003-2170-5432.

******* Institute for Emergency Medicine of the Primorsko-Goranska County, Rijeka, Croatia. ORCID ID: https://orcid.org/0000-0001-7503-2259.

Correspondence Address: Gordana Pelčić, University of Rijeka, Faculty of Medicine, Department of Social Sciences and Medical Humanities, B. Branchetta 20, Rijeka, Croatia. Email: gordana.pelcic@medri.uniri.hr.

of facing parental vaccine hesitancy are primary care pediatricians. They can testify their own limiting abilities to do so, as well as the limiting abilities of other professionals involved in vaccinology. In the situation of an enormous amount of data, they could be drowned out and interpreted in various ways. It is clear that the old-fashioned "defense" of the great public achievement of the 20 century - vaccinology - is no longer appropriate. On the other hand, a search of the literature shows the entry of "Big Data" into medicine in general and the public health and vaccinology. This paper attempts to position the role of Big Data (its benefits, traps, and ethical implications) in vaccinology in the 21st century based on the literature research and our propositions.

Keywords: vaccinology, Big Data, ethics of Big Data, immunization practices.

1. Vaccinology

Vaccination is a "public health intervention aimed at preventing infection related to mortality, morbidity and disability"[1]. As Delany stressed[2], the story of vaccinology started in 1721 with the introduction of variolation from Asia to Europe. The first vaccine against smallpox was introduced in 1796. By the end of the 20th century, vaccination became the procedure of the highest achievements of public medicine. This achievement helps "build a society free of vaccine-preventable diseases and save lives of millions of children across the globe"[3]. Regardless of the facts which support vaccination programs, we have suboptimal coverage rates, especially among the vulnerable population, such as preterm infants, newborn, oncology patients, pregnant women, patients with the immune-related disease, elderly people, etc[4]. The world entered the 21st century with the first therapeutic vaccine and reverse vaccinology in 2013. The development of vaccine shifts from reductionists towards the holistic approach or system biology[5] trying to predict immunogenicity after the vaccination by the computational help. It is estimated that the vaccination program

1 Bragazzi, N.L., Gianfredi, V., Villarini, M., Rosselli, R., Nasr, A., Hussein, A., Martini, M., Behzadifar, M. (2018), Vaccines Meet Big Data: State-of-the-Art and Future Prospects, From the Classical 3Is ("Isolate-Inactivate-Inject") Vaccinology 1.0 to Vaccinology 3.0, Vaccinomics, and Beyond: A Historical Overview. *Front Public Health,* 6, 62.

2 Delany, I., Rappuoli, R., De Gregorio, E. (2014), Vaccines for the 21st century, *EMBO Mol Med*, 6 (6), 708–20.

3 Delany, I., Rappuoli, R., De Gregorio, E. (2014), 708–20.

4 Cotugno, N., Ruggiero, A., Santilli, V., Manno, E.C., Rocca, S., Zicari, S., Amodio, D., Colucci, M., Rossi, P., Levy, O., Martinon-Torres, F., Pollard, A.J., Palma, P. (2019), OMIC Technologies and Vaccine Development: From the Identification of Vulnerable Individuals to the Formulation of Invulnerable Vaccines, *J Immunol Res*, 2019, 8732191.

5 Blohmke, C.J., O'Connor, D., Pollard, A.J. (2015), The use of systems biology and immunological big data to guide vaccine development, *Genome Med*, 7, 114.

saves over 3 million lives of children per year[6] as well as saves millions of dollars of the health care cost[7] that could be used otherwise.

The new social moments in 21st-century life with globalization, economic growth, immigrations, and new infections have to lead to a new vaccination paradigm.

Despite all the scientific data regarding the benefits of vaccination for our lives, vaccination medicine is one of the most questioned procedures in medicine in the last couple of decades. There are anti-vaccine movements across the globe, and the hesitancy of parents rises every day. The immunization has been accused as the cause of different types of adverse reactions: allergic reactions, cause of autoimmune diseases, autism, and much more[8]. Vaccinology crosses the path "from the lifesaving procedure" to the most questionable procedure in medicine in a very short period. The science is on one end, and the anti-vaccination movement's unverified information is on the other end of the vaccinology story. There are many reasons for suboptimal vaccine coverage, but we can summarize them in two; most of the physicians have not had the chance to see or treat a child with a vaccine-preventable disease, such as diphtheria or poliomyelitis, and the second reason is that there is a suspicion regarding the efficacy and safety of the vaccine[9].

Lately, we have been witnessing that anti-vaccine-oriented visitors of symposia dedicated to vaccination turn the discussion towards the necessity of explaining fundamental medical knowledge. A similar thing occurs during the public presentation of immunization. There is an impression that we have turned back to explaining the elementary level of knowledge regarding preventable childhood diseases and their impact on children's lives and health. The globalization in health care on the one side and great technological achievements, on the other side, creates the possibilities where an enormous amount of data is publicly available. The source of those data is the product of a large scientific work area from all fields of human knowledge. On the other hand, a significant amount of data came from activities of social infrastructure[10]. There is a question of how we can navigate through the enormous amount of data regarding the vaccination? To which data should we trust, to which we should not trust? Who posted those data on the Internet? Which review is representative, which is not? Bragazzi et al., in their paper, emphasize that information and communication technologies can positively influence parental vaccine-related

6 André, F.E. (2003), Vaccinology: past achievements, present roadblocks and future promises, 21 (7-8), 593–5.

7 Brennan, B. (1998), Vaccines: the wave of the future, *Perspect Health*, 3 (2), 17–21.

8 André, F. E. (2003), 593–5.

9 Cotugno, N. Et al. (2019), 8732191.

10 Vayena, E., Blasimme, A. (2017), Biomedical Big Data: New Models of Control Over Access, Use and Governance, *J Bioeth Inq*, 14 (4), 501–513.

knowledge, attitudes, beliefs, and vaccination willingness[11]. Sometimes the impression is that the negative connotation on vaccination (regardless of its relevance) reaches better the general audience better. To keep the welfare of vaccination on the life and health of children and population in general, to prevent returning to times when the preventable childhood disease has taken millions of children's lives, the necessity of reachability, understanding, and organization of scientific information regarding the vaccination has been raised. For example, medical agencies (FDA - Food and Drug Administration, EMEA – European Medicine Agency, HALMED Croatian Agency for Drugs and Medical Products, etc.) collect the data regarding the adverse reactions to vaccination. In other words, we have respectable Big Data regarding the adverse reaction to vaccination. The professionals had to find a way to make Big Data available and easily accessible to the general population, pediatricians, or other interested parties. Google Trends can be used to monitor how often people search the Internet for information regarding the vaccination, or it can help us see if the search was spontaneous or induced by media, or give us information regarding the specificity of information that was searched [12]. Based on this kind of information, a specialist can address the parents and the public with the specific information that they seek.

The literature search shows the entry of "Big Data" in medicine in general and in public health and vaccinology. We searched mainly database *PubMed* for the search topics "Vaccination and Big Data", "Immunization and Big Data", and "Big Data". A group of experts by consensus selected the papers we used in this work[13]. This paper is an attempt to position the role of Big Data (its benefits, traps, and ethical implications) in vaccinology in the 21st century based on exploring the literature and our propositions regarding the same.

2. Big Data

We all witness a huge amount of data circulating each second. The data are created, gathered, and processed[14]. The appearance of Big Data is due to the digitalization in

11 Bragazzi, N.L, Barberis, I., Rosselli, R., Gianfredi, V., Nucci, D., Moretti, M., Salvatori, T., Martucci, G., Martini, M. (2017) How often people google for vaccination: Qualitative and quantitative insights from a systematic search of the web-based activities using Google Trends, *Hum Vaccin Immunother*, 13 (2), 464–469.

12 Ibid, 464–469.

13 Ibid.

14 Vayena, E., Blasimme, A. (2017), 501–513.

everyday life and health care settings, on the one hand. On the other hand, is the emergence of computational analytic techniques[15].

The expression "Big Data" was introduced by Roger Margoles[16] in order to explain the situation of overloading the web with a huge amount of data measured in exabytes 1018 and zettabytes 1021. There are many definitions of Big Data. One of the definitions states that they are "datasets whose size is beyond the ability of typical database software tools to capture, store, manage, and analyze"[17]. Costa defined Big Data as "a new generation of technologies and architectures, designed to extract value from large volumes of a wide variety of data by enabling high-velocity capture, discovery, and analysis"[18]. More recently, the HMA-EMA Joint Big Data Taskforce has defined Big Data as "extremely large datasets which may be complex, multi-dimensional, unstructured and heterogeneous, which are accumulating rapidly and which may be analyzed computationally to reveal patterns, trends, and associations. In general, big data sets require advanced or specialized methods to provide an answer within reliable constraints"[19].

Big Data may be characterized by three V-s: Volume, Variety, and Velocity[20]. *Volume* - the great amount of information presents the challenge for creating a model for storing these data. The *Variety* of data emphasizes that data can be "structured", "semi-structured", or "unstructured". *Velocity o*r data in motion refers to the speed with which data are generated. The *Value* of data is characteristic of Big Data technology structured to extract value from the enormous extent of different data. The last V stands for the *Veracity* of data characterized by Accuracy, Certainty, and Precision[21].

Big Data interfere with various segments of our lives, such as business, science, government, national security, transports, health care[22], social science, pleasure, etc.

15 Ienca, M., Ferretti, A., Hurst, S., Puhan, M., Lovis, C., Vayena, E. (2018), Considerations for ethics review of big data health research: A scoping review, *PLoS One*, 13 (10), e0204937.

16 Emani, C.K., Cullot, N., Nicolle, C. (2015), Understandable Big Data: A survey, *Computer Science Review*, 17, 70–81. Available at https://www.cs.helsinki.fi/u/jilu/paper/bigdatasurvey01.pdf (Accessed: 8 October 2019)

17 Manyika, J., Chui, M., Brown, B., Bughin, J., Dobbs, R., Roxburgh, C., Hung Byers, A. (2011), Big data: The next frontier for innovation, competition, and productivity, McKinsey Global Institute, available at https://www.mckinsey.com/~/media/McKinsey/Business%20Functions/McKinsey%20Digital/Our%20Insights/Big%20data%20The%20next%20frontier%20for%20innovation/MGI_big_data_exec_summary.ashx, (Accessed: 6 October 2019).

18 Costa, F. (2014), Big data in biomedicine, *Drug Discov Today*, 19 (4), 433–40.

19 European Medicine Agency. HMA-EMA Joint Big Data Taskforce. Summary Report EMA/105321/2019, 2019.

20 Hitzler, P., Janowicz, K. (2013), Linked data, big data, and the 4th Paradigm, Semantic Web 0 (0), 1, Available at http://www.semantic-web-journal.net/system/files/swj488.pdf, / (Assessed: 8 October 2019); Manyika, J., Chui, M., Brown, B., Bughin, J., Dobbs, R., Roxburgh, C., Hung Byers, A. (2011).

21 Manyika, J. et al. (2011).

22 Ienca, M. et al. (2018), e0204937.

DIKW hierarchy (Data, Information, Knowledge, and Wisdom)[23] could be applied in the area of Big Data.

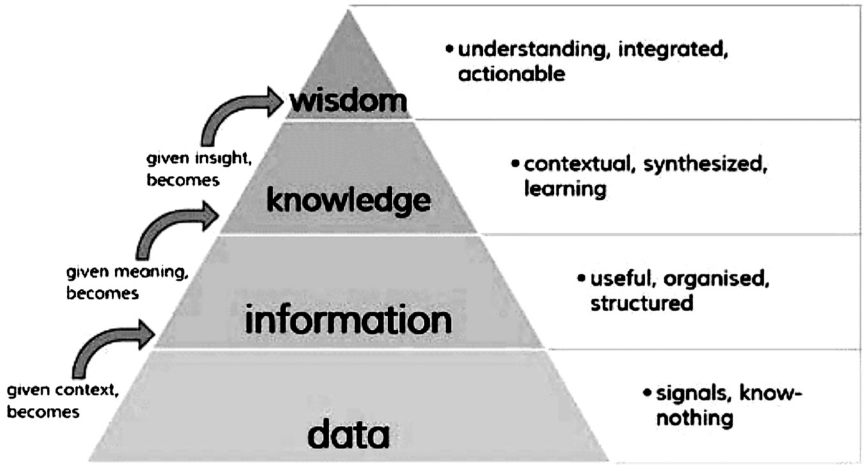

Figure 1: The DIKW pyramid
Source: Soloviev, K., (2016)[24]

The knowledge hierarchies represent the process of transformation of a concept from a lower level to the concept or entity on a higher level[25]. In the knowledge hierarchy[26] (Figure 1), the data are symbols that represent the properties of objects. The data are results of observation with no value by itself[27]. The data have various forms and various origins. To fulfill the mission, data have to be true. As Frické mentioned, data are created for a particular purpose limiting their usefulness in other situations. The next step in the pyramid is information. This is the step where data are processed and become information. In the process of processing data, some of the data are lost. The information can answer the questions about what, where, and when[28]. In the DIKW pyramid, the semantic information is essential for the "Weak knowledge" in this case. The next step has brought us to the level of knowledge, the level at which

23 Frické, M. (2009), Knowledge pyramid, The DIKW hierarchy, *J INF SCI*, 35 (2), 131–142; Rowley, J. (2007), The wisdom hierarchy: representations of the DIKW hierarchy, *J. Inf. Sci*, 33 (2), 163–180.

24 Soloiev, K. (2016), 3 Steps to a Data-Driven Content Quality Approach. Exploring the role of Big Data in Official Statistics, Available at http://blog.contentquo.com/blog/3-steps-to-data-driven-quality-approach/, (Accessed: 3 November 2019).

25 Rowley, J. (2007), 163–180.

26 Soloiev, K. (2016), 3 Steps to a Data-Driven Content Quality Approach. Exploring the role of Big Data in Official Statistics, Available at http://blog.contentquo.com/blog/3-steps-to-data-driven-quality-approach/, (Accessed: 3 November 2019).

27 Zhang, G.L., Sun, J., Chitkushev, L., Brusic, V. (2014), Big data analytics in immunology: a knowledge-based approach, *Biomed Res Int*, 2014, 437987.

28 Ibid.

we know-how, which gives us the answer to how and why. At this point, information becomes instruction. The last level in the DIKW pyramid is wisdom, which includes mental component and could never be automatized and could never occur without a human. The wisdom is called wide knowledge, the point of knowledge for practical and ethical problem-solving. According to Ackoff[29], wisdom includes values and judgment. Our schooling is not based on the development of judgment nor the generation of information. Humankind, unfortunately, learns to reach wisdom in a hard way. These were the words Ackoff said in 1999. The digitalization of human life twenty years later confirmed these words even more. The amount of each DIKV pyramid level in our lives decreased from the bottom of the pyramid to the top. We are surrounded by a huge amount of data that do not mean anything.

3. Source of Big Data

The origin of Big Data has an enormous, unprecedented width. It comes from heterogeneous sources[30]. A part of these data comes from the scientific area, a part of them comes from government activities, part of them comes from the non-government sector, and a part of them comes from social activities, individual activities, interest groups, etc. The data can be available on the Internet, TV, or paper media. The author of data can be traced or known, or the author could not be traceable. Assuming we try to imagine possible ways of all the availability of our data (social, professional, financial, health, emotional, entertainment, sport), we can conclude that each of us can hardly have control over our data.

Biomedical data are made up of phenotypic, genotypic, behavioral, and environmental data[31].

The chart of Vayena, Dzenowagis, and Langefeld, named "Evolving health data ecosystem", systematically presented the possible origin of "biomedical big data" [32], such as health services, public health activities, biomedical research, data derived from exposure to environmental factors, data from lifestyle and socioeconomic conditions, data derived from behavioral and social habits. The authors list the stakeholders, such as individuals and groups, health services, academia and research, health care industry, data ITC industry, and government.

29 Ackoff, R. (1999), From data to wisdom. Ackoff's Best, New York, Joh Wiley§ Sons 170–172, http://faculty.ung.edu/kmelton/Documents/DataWisdom.pdf (accessed: 5 November 2019).

30 Ienca, M. et al. (2018), e0204937.

31 Vayena, E., Blasimme, A. (2017), 501–513.

32 Vayena, E., Dzenowagis Jand Langefeld, M. (2016), Evolving health data ecosystem, World Health Organization, https://www.who.int/ehealth/resources/ecosystem.pdf, (Accessed: 8 October 2019).

This information can have an impact on an individual and population level. The impact can be positive, hopefully, useful for improving the health care of individuals and the population. However, on the other hand, it could have negative connotations, such as manipulation on an individual or population level.

What is the situation regarding our health data? Where can personal health data be found?

What is with the "national" health data?

Big Data can be used or tracked from social media platforms, such as Twitter for the prognosis of the disease, or Facebook for prevention of suicide, for checking seasonal pollen calendar, or for managing asthma[33].

4. Ethics of Big Data

The data growth to the level of billion gigabytes irreversibly changes their morality, socio-economic status, and epistemic status[34]. Big Data technologies raise ethical concerns and questions. The ethical quality[35] of Big Data is the amount of data, which is the largest in the history of humankind, and it comes to 2015-5-billion gigabytes every 10 seconds; the organic attribute of Big Data – while collecting every digital data better represents reality; the globality of Big Data enables global benefit; Big Data emphasizes the correlation of data over the cause of data. Data access, data privacy, and data validation in clinical trials are the biggest challenges that need ethical guidelines[36].

Privacy, personal autonomy, and solidarity could be compromised in relation to Big Data nowadays[37].

Privacy becomes hard to protect. It is almost impossible to achieve the anonymization of Big Data. The ethical question is raised regarding the ability to analyze Big Data towards planning the tendencies of some persons, such as the tendency to be a criminal before committing a crime. Big Data helps us in education and study on the one hand, but while using it to collect new knowledge and write a new paper, we cannot know how to protect our digital fingerprints. Last year, the EU's High-Level

33 Ienca, M. et al. (2018), e0204937.

34 Lipworth, W., Mason, P.H., Kerridge, I. (2017), Ethics and Epistemology of Big Data, *J Bioeth Inq*, 14 (4), 485–488.

35 Zwitter, A. (2014), Big Data Ethics, Big Data§ Society, July-December, 1–6. https://journals.sagepub.com/doi/pdf/10.1177/2053951714559253, (Assessed: 8 November 2019).

36 Ienca, M. et al. (2018), e0204937.

37 Vayena, E., Salathé, M., Madoff, L.C., Brownstein, J.S. (2015), Ethical challenges of big data in public health, *PLoS Comput Biol*, 11(2), e1003904.

Expert Group on Artificial Intelligence published "Ethical Guidelines" with the most important "requirements which AI systems should meet", including privacy and data governance[38].

For generations, informed consent was a successful tool in protecting health care data accompanied by autonomy, privacy, and trust[39]. With the growth of the online world, the old famous informed consent started to lose control over human values of privacy and confidentiality. To protect these values, humankind needs a new approach. Vayena and Blasimme offer three approaches to those fundamental values: data portability rights, in terms of data access control, a new model of informed consent, in terms of data usage control, and participatory data management, in terms of data control by way of involvement in data governance.

The protection of Big Data is questionable on the personal and institutional level. How can we protect our biomedical data? On the primary health care level, there are computational programs for the storage of health care data. The patient, himself/herself, gives data to the physician. There are data regarding the diagnostic results, regarding the physicians' clinical observation, there are also data that come from other medical professionals, such as conciliar exams, and community nurse. The patients should have access to these data, the primary care physician should also have access, and some other health care professionals should have access if the patient gives his/her permission. In addition to them, there are other employees in this office. There is informatics back up of the institution. There are controlling managers of the institution where the primary health care doctor works, unknown people who manage the whole software, and controllers of health care institutions. It is obvious that the individual patient cannot control their health care data. If we ask ourselves, for example, who is responsible for controlling, managing, or accessing these data, it is hard to find an exact answer. The situation is similar at the level of secondary and tertiary health care. Only in these situations it is more difficult to secure the control of Big Data in health care.

How can Vayena et al.'s three models of data control, use, access, and governance be applied in the mentioned situation is hard to imagine. It requires specific computer abilities, knowledge, and legal framework for a start.

If we speculate about adding some other data on the previously mentioned, the illusion of data control is bigger and more realistic, as Brandimarte et al. discussed in

38 High-Level Expert Group on Artificial Intelligence (AI HLEG), https://ec.europa.eu/digital-single-market/en/high-level-expert-group-artificial-intelligence.

39 Vayena, E., Blasimme, A. (2017), 501–513.

their article[40]. A similar situation occurs regarding the ownership of biomedical Big Data. The control of Big Data and the secondary use of data are ethical challenges nowadays[41].

The position of Ethics committees in the contents of Big Data should be revaluated. The guidelines regarding the approval of research, which needs access to millions of personal data, should be created. Lence et al., in their review, show that only 13% of evaluated papers provided a specific normative recommendation for ethic committees[42]. There are real possibilities of de-identification of previously anonymized data. The anonymized data in the era of Big Data (digitalized data) and computational possibilities of analyzing those data become a utopia.

The computational and methodological abilities of members of ethics committees are questioned because, without them, the members of ethics committees will not be able to resolve the ethical challenges of Big Data in health care settings[43].

The big ethical question is the knowledge of particular physicians and particular patients regarding the world of Big Data. In the term of the world, we allude on the comprehensive amount of the Big Data available to help patients. A part of IT knowledge and possibilities scare us more. The physicians are not educated regarding the computational possibilities; they are not educated regarding the statistical possibilities. The methodology for exploring the possibilities of Big Data is unknown to us. Physicians are not computational people, they are not statistical people, but they are responsible for respecting ethics and law to protect patients' health care data. For example, in the Health Care Centre of Primorsko Goranska County, in which the first author of this article works as a pediatrician, as in other health care institutions throughout the world, the medical professionals had to sign the paper regarding the privacy of patient health care information. In the previous paragraph, we mentioned the known, and we imagine the unknown individuals who have access to health care information. It seems that average physicians today should be educated in computational and methodological fields to be able to use the benefits of Big Data in the treatment of their patients. Due to the gathered information, the question is whether the medical study's computational professional would be a better solution for the patients in the area of healthcare-oriented Big Data.

40 Brandimarte, L., Acquisti, A., Loewenstein, G., Babcock, L. (2009), Privacy Concerns and Information Disclosure: An Illusion of Control Hypothesis, IDEALS, https://www.ideals.illinois.edu/bitstream/handle/2142/15344/Privacy_concerns_and_information_disclosure.pdf?sequence=2&isAllowed=y, (Accessed: 23 October 2019).

41 Ienca, M. et al. (2018), e0204937.

42 Ibid.

43 Ibid.

5. Big Data in health care

Emerging of Big Data in health care settings can result in preventive, diagnostic, and therapeutic benefits[44] from medical blogs and health records.

The health care data can be derived from Electronic Health Records, mobile health applications and web-networks, health care robotics, medical internet, direct-to-consumer genetics, and screening tests[45]. The source can also be a nonmedical data source, such as personal dietary programs, fitness club membership, etc.

The potential positive impact of Big Data on clinical settings is enormous, such as the creation of epidemiological models, continuous monitoring of patient's health, and the benefit in public and individual health. Ienca et al. reviewed the literature from 2012-2017 regarding the article on health related to Big Data. Their results show that the number of such articles is 131 times higher than in the period 2001-2005[46]. The authors show potential benefits in the research, preventive medicine in individual cases and at the public level, in clinical medicine, such as personalized medicine, diagnostics, clinical decision-making, health monitoring, and improving patient safety and therapy.

In this study, seven challenges arise regarding the Big Data in health care settings:

a. Technical challenges in the sense of data security, data quality, data storage, data linkage, and data reuse.

b. The methodological challenge in the sense of methods used in the study, standardizing the data and metadata, collecting and processing the data, monitoring the usage of data.

c. The regulatory challenge in the sense of directive regarding the ownership of data, detecting the potential risk with using and managing the data.

d. The social challenge in the sense of relevance for human society and the members of human society.

e. Infrastructural challenges in the sense of possibilities of existing infrastructures.

f. The financial challenge in the sense of financial possibilities of data storage sites.

g. Ethical challenges in the sense of moral principles. The privacy and confidentiality issue, informed consent, fairness and justice, trust and data ownership were most examined.

44 Ienca, M. et al. (2018), e0204937.

45 Ibid.

46 Ibid.

Table 1: The terms and the definition of the terms used in paper

Term	Definition
Big Data[47]	"Large sets of data" with different level of structuration, emanating from different sources, "produced with high frequency" and further processed and analyzed by computational techniques.
Biomedical Big Data[48]	All health-relevant data that can be used for health-related purpose.
"Omics" Tehnologies[49]	"Quantitative measurements on a global scale and provide the ability to interrogate more than just the genome or transcriptome. The ability to comprehensively probe the proteome, metabolome, interactome, fluxome, lipidome, imflammasome".
Vaccinomics[50]	"The application of immunogenetics and immunogenomics to the study of vaccine-induced immune response".
Adversomics[51]	"The application of immunogenomics and systems biology approaches to understand the genetic and non-genetic drivers of vaccine adverse reactions at the molecular level."
Reverse vaccinology[52]	"The use of genomic data and in silico analyses to rapidly identify antigens for vaccine use".
Systems vaccinology[53]	"The application of systems biology methods to understanding and predicting vaccine-induced immune responses".
Personalized vaccinology[54]	"Optimal personalized vaccine approach, consisting of an optimal vaccine formulation, route of administration, adjuvant, dose, and dosing schedule (for vaccines that require multiple doses) for an individual or group of individuals".
Genomics[55]	Systemic, genome-wide investigation of genes

47 Ienca, M. et al. (2018), e0204937.

48 Vayena, E., Blasimme, A. (2017), 501–513.

49 Kennedy, R.B., Poland, G.A. (2011), The top five "game changers" in vaccinology: toward rational and directed vaccine development, *OMICS* 15 (9), 533–7.

50 Ibid.

51 Whitaker, J.A., Ovsyannikova, I.G., Poland, G.A. (2015), Adversomics: a new paradigm for vaccine safety and design, *Expert Rev Vaccines*, 14 (7), 935–47.

52 Poland, G.A., Kennedy, R.B., McKinney, B.A., Ovsyannikova, I.G., Lambert, N.D., Jacobson, R.M., Oberg, A.L. (2013), Vaccinomics, adversomics, and the immune response network theory: individualized vaccinology in the 21st century, *Semin Immunol*, 25 (2), 89–103.

53 Maure, C.G., Dodoo, A.N., Bonhoeffer, J., Zuber, P.L. (2014), The Global Vaccine Safety Initiative: enhancing vaccine pharmacovigilance capacity at country level, *Bull World Health Organ*, 92 (9), 695–6.

54 Whitaker, J.A., Ovsyannikova, I.G., Poland, G.A. (2015), 935–47.

55 Bragazzi, N.L. et al. (2018), 62.

6. The place of Big Data in Vaccinology

As we mentioned earlier, vaccination saves millions of lives worldwide. Despite this, there are still unrealized protections from various infections, such as pandemic of HIV, TB[56] on the one hand. On the other hand, vaccine hesitancy and anti-vaccine movements question the great success of vaccinology in the past.

The 21st century faces a new approach in the research and development of a vaccine. The outdated approach "Isolates, Inactivates and Injects" and "one fits for all" is excepted to be replaced with "person to person" and "Population to population" specificity in vaccinology[57]. Kennedy and Poland introduce five components of vaccinomics, a new term for creating a safe and effective vaccine. One of them is Bioinformatics and Data Analysis. The research and omics in vaccinology development are accompanied by a variety of huge amounts of data. It is necessary to have informatics and statistic logistics to organize and analyze such data in order to be useful and beneficial in the production of the vaccine. Nakaya et al. emphasize the collaboration of immunologists and computational scientists to generate data-driven hypotheses to clarify the mechanisms of protective immunity[58].

Bragazzi et al. give us the list of potential benefits of Big Data in vaccinology[59].

a. The role of Big Data in vaccine discovery and design. As an example, they cite Bexero, the commercial name for a vaccine against *Neisseria meningitides*. The Bexero is an example of a web-based vaccine that was designed with the help of computational tools and algorithms, such as SORT, PSI_BLAST, and FindPatterns[60].

b. The place of Big Data in vaccine production and delivery. The pharmaceutical companies and computational companies together try to identify possible negative interference in the cold chain of vaccine transportation.

c. The Vaccine campaigns could help Big Data with the prediction of epidemiological figures or monitoring the success of vaccine campaigns. The use of novel data streams today seems to belong more to the anti-vaccine movements than to the scientists who promote vaccination programs. It appears that scientists are closed into a narrow circle of people.

56 Nakaya, H.I., Pulendran, B. (2015), Vaccinology in the era of high-throughput biology, *Philos Trans R Soc Lond B Biol Sci*, 19, 370(1671).

57 Bragazzi, N.L. et al. (2018), 62; Kennedy, R.B., Poland, G.A. (2011), 533–7; Poland, G.A., Ovsyannikova, I.G., Kennedy, R.B. (2018), Personalized vaccinology: A review, *Vaccine*, 36 (36), 5350–5357.

58 Kennedy, R.B., Poland, G.A. (2011), 533–7.

59 Bragazzi, N.L. et al. (2018), 62.

60 Ibid, 62.

d. Big Data can be used in the monitoring of vaccine efficacy. There are different possibilities in doing so. One possibility is to collect data regarding the outbreaks of preventable diseases.

e. The Benefit of Big Data in Vaccinology can be demonstrated in the collection of side effects of vaccination. Serious immunological reactions are very rare[61]. In March 2012, the World Health Organization (WHO) initiated the Global Vaccine Safety Initiative with the aim of creating a global support structure for vaccine safety[62] by creating a network of countries across the globe to detect and analyze adverse reactions. This initiative could help monitor public concern regarding the vaccination with the aim to predict and plan the potential intervention.

   However, their effect on public perception regarding the vaccination has multiple negative connotations. Every physician has a duty to report a side effect of a medicine. The same is with the vaccine. The patients also have the opportunity to report side effects. If we imagine the amount of data on the vaccine's side effects reported to FDA, EMA or in Croatia to HALMED and to other medical agencies, we have an enormous amount of data, which represent worldwide data particular product's side effects. The amount is in a million data information on, for example, MoPaRu side effects. The circle would be closed if each physician and patient could have such information on a regular basis. There are such data available, but we are often not aware of them, and we do not use them to confirm the information that is of unknown origin or origin that is not based on scientific ground.

   At this point, we would like to refer to the DIKW pyramid in the condense of anti-vaccine movements last decades. From basic science through clinical research, which ended with a particular vaccine in a pediatric office, scientists used huge amounts of data trying to build a particular vaccine against the causative agent of a specific disease. In this process, they use achievements achieved in the past, as well as setbacks experienced in the past, today's achievements and experiences, novel possibilities, the help of medicine, the help of computing professionals to create a vaccine beyond one fit for more.

f. The place of Big Data in vaccine hesitancy. Big Data can help scientists in tracking the elements that push parents to vaccine hesitancy. By exploring those elements, the professionals can give correct answers to patients' questioning and fear.

61 Stone, C.A. Jr, Rukasin, C.R.F., Beachkofsky, T.M., Phillips, E.J., (2019), Immune-mediated adverse reactions to vaccines, *Br J Clin Pharmacol* . doi: 10.1111/bcp.14112. [Epub ahead of print]

62 Maure, C.G., Dodoo, A.N., Bonhoeffer, J., Zuber, P.L. (2014), 695–6.

We witness today that there are patients who do not have an adequate immune response to vaccination. We are not able to predict who will have serious adverse reactions to vaccination. The history of vaccine development is empirical. The paradigm one fits for all is based on ignorance of the complexity of the human immune system and host genome[63]. This situation helps in spreading anti-vaccine movements globally. The emphasis of the anti-vaccine movement is placed on serious adverse reactions, on the one hand, and vaccine ineffectiveness, on the other, pushing aside the facts of a million lives saved among the pediatric population since the beginning of the vaccinology era.

The values of analysis of Big Data or high-dimensional data in vaccinomics are elaborated by Oberg et al.[64]. The generation, analysis, and modeling Big Data can be useful in the prediction of vaccine responses. Personalized vaccinology is directed to the right vaccine for the right patient in an appropriate time to prevent the disease while staying free of the vaccine sides effect. This scenario would be ideal for patients and for physicians at the same time. To achieve this goal, it is very important to make an appropriate study design, chose the exact antibody level, predict the occurrence of the immune response, etc. The important component in vaccinomics is adequate statistical modeling, which can detect possible associations between phenotype properties and explanatory variables.

Poland et al.[65], in the review, elucidate the meaning of personalized vaccinology. Current knowledge in vaccinomics and adversomnics helps to understand and provide answers on how to identify a patient with a higher risk of infection, or who has a higher risk for inadequate immunogenicity or serious adverse reactions, or how to determine the optimal vaccine dose for an optimal immunological response. The resulting solution leads us to personalized vaccinology in the future. To predict the personalized vaccine, it is necessary to assess genetic background, sex, and some other factors, such as age, weight, race, or medical condition. Cotugno et al. emphasize the necessity of personalizing vaccination in a vulnerable population[66] because of their weaker vaccine-specific immunity response, such as antibody production in transplanted patients.

Poland et al.[67] have offered the first mathematical model and predictive equitation for predetermined immune response:

63 Poland, G.A. et al. (2013), 89–103.

64 Oberg, A.L., McKinney, B.A., Schaid, D.J., Pankratz, V.S., Kennedy, R.B., Poland, G.A. (2015), Lessons learned in the analysis of high-dimensional data in vaccinomics, *Vaccine*, 33 (40), 262–70.

65 Poland, G.A., Ovsyannikova, I.G., Kennedy, R.B. (2018), 5350–5357.

66 Cotugno, N. et al. (2019), 8732191.

67 Poland, G.A. et al. (2013), 89–103.

$$y = \beta_0 + \sum_{i=1}^{p} \beta_i x_i + \varepsilon$$

y measure of a person's immune response

β_0 is the intercept

β_i is the coefficient or slope for the ith variable

x_i and indicates the amount of change in y for a 1unit change in x_i

ε random deviations from this model

By creating the "right" equation, scientists could be more rapid, direct, and rational in the development of a new vaccine that would be effective, safe, and without side effects.

To recognize genetic variants that can influence adaptive vaccine induced immune response. The polymorphism of HLA, KIR, MICA, and BTN genes have an influence on the immune response to immunization against several diseases (influenza, smallpox, and hepatitis B)[68]. It is known that there are sex differences in the humoral and cellular immune response to the vaccine and indicate that adverse reactions are higher in the female. The mechanism that causes sex differences in the immune response is not well known[69]. Obesity is one factor that is connected with impaired immunogenicity.

The adversomics with the goal of identification, characterization, and prediction of adverse reaction could be one of the answers to anti-vaccine movement. If we could predict maladaptive immune response that could cause the damage in the host, we would avoid such a vaccine[70]. Berkovic et al.[71] give an example of sodium channel gene SCN1A mutation in possible vaccine encephalopathy. They studied 14 patients with alleged vaccine encephalopathy that occurred after the first of three dosed of diphtheria- pertussis – tetanus and diphtheria -pertussis- tetanus –inactivated polio – Haemophilus influenzae type b vaccine in infancy. In the 9 of 11 cases, the investigator found de novo mutation. The epidemiological studies did not correlate encephalopathies and vaccine, while the individual cases indicated so.

Adjuvants in vaccine production have been placed in a vaccine hesitancy environment as a negative component. In contrast, Cotugno et al. gave examples where the development of adjuvants can enhance immune response[72]. Adjuvant

68 Cotugno, N. et al. (2019), 8732191.

69 Poland, G.A., Ovsyannikova, I.G., Kennedy, R.B. (2018), 5350–5357.

70 Ibid.

71 Berkovic, S.F., Harkin, L., McMahon, J.M., Pelekanos, J.T., Zuberi, S.M., Wirrell, E.C., Gill, D.S., Iona, X., Mulley, J.C., Scheffer, I.E. (2006), De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurology*, 5 (6), 488–92.

72 Cotugno, N. et al. (2019), 8732191.

development and OMICS technologies can increase the knowledge regarding the vaccine hyporesponsiveness.

On the way to personalized vaccinology, the scientists have to overcome the following challenges[73]: larger genotype: phenotype datasets, integration of Big Data, consider in addition to the humoral immune, the cellular immune response; upgrade of biostatistical and bioinformatics approach; overcome financial difficulties in low and middle-income countries.

If we analyze the anti-vaccine movement arguments, we face a level of data or information. It is hard to achieve a level of wisdom in explaining why not use a vaccine. The whole anti-vaccine movement is often shrouded in conspiracy theories, in which case the reason to argue on the level of knowledge and wisdom stops because of the conspiracy. The shocking information regarding the side effects of vaccines, the shocking web pages with a picture of a skull and a syringe, which represent vaccines, are data for which we are not sure whether they are true or not. Furthermore, we are unable to track the origin of such data. They are often not processed into information or knowledge or wisdom. However, they shockingly fulfill their purpose.

As the process of debating the vaccine issue goes on, both sides arguing without wisdom jeopardize the historical achievements of vaccinology in our lives. Hinman and Orenstein propose new action and new strategies to achieve the Global Vaccine Action Plan (GVAP)[74]. The new GVAP is necessary to respond to the global burden of vaccines today.

Vaccinology is not a dogma; we should be able to discuss different issues on the topic, trying not to argue on the level of data.

The language of Big Data

The use of language is related to the communication between the patient and the physician. In this communication, the physician is in a superior position due to the knowledge of both the topic and the terminology. On the other hand, the patient is always in a subordinate and inferior position, as his/her knowledge of the topic and the topic related terminology is limited[75]. It often leads to a misunderstanding, which is the result of the unequal language competence of interlocutors. With the entry of Big Data in medicine in general, we should switch our minds and abilities towards

73 Poland, G.A., Ovsyannikova, I.G., Kennedy, R.B. (2018), 5350–5357.

74 Hinman, A.R., Orenstein, W.A. (2017), Collaborating to achieve Global Vaccine Action Plan goals, *Lancet*, 390 (10093), 451–452.

75 Nikolić-Hoyt, A. (2003), Semantička adaptacija engleskih posuđenica u hrvatskom jeziku, *Filologija*, 41, 169–184.

the new communications. We have new parties in the communication process, the computational scientists with their own language and their way of communication. In order to transfer data and knowledge from the world of computational science to the world of medicine, both doctors and patients could be in a subordinate position. The availability of Big Data in vaccinology could be jeopardized because of a lack of abilities to understand the language of computational science.

7. Conclusion

The essence of the term Big Data can hardly be imagined in our everyday lives. Without computational knowledge, the amount of data available on a particular issue, such as in this paper on vaccinology, is hard to comprehend. Big Data in health care settings and vaccinology provide us with a great opportunity to improve vaccination effectiveness and reduce the vaccine's side effects. As we stressed in the paper, the adversomics is one of the "branches" of Big Data that is very important today. The worldwide population is uncertain regarding the possible side effects of the vaccine. The use of Big Data in the analysis of the possible side effects and later in the production of vaccines, which can avoid the appearance of these side effects, would be a great achievement of Big Data in vaccinology. Another important issue of Big Data in vaccinology is personalized vaccinology that avoids the old paradigm *one fits all*. Big Data could help us develop technologies to produce vaccines considering sex, weight, gene, phenotypes, etc.

There are many other possibilities that vaccinology can gain from Big Data, for example, through epidemiological studies, to create a campaign for successful vaccination. Anti-vaccination movements are powerful today[76]. Vaccine hesitancy was listed among the ten most significant threats to global health by the World Health Organization in 2019[77].

The size of Big Data extends the size of data that used to be available in the previous studies. Without computational science, Big Data regarding vaccinology would stay on the bottom level of knowledge information, on the level of data. We need the computational knowledge to collect data, analyze and create, and conclude or correlate among those data. The involvement of different experts in areas once dedicated only to medical professionals could present an ethical dilemma in the future.

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76 Tucak, I. (2017), Obvezno cijepljenje djece: za i protiv, in: Rešetar, Branka et al. eds., *Suvremeno obiteljsko pravo i postupak*, Obiteljskopravna biblioteka, Pravni fakultet Osijek, 137–165.

77 World Health Organization. Ten threats to global health in 2019. https://www.who.int/news-room/feature-stories/ten-threats-to-global-health-in-2019, (Accessed: 23 October 2019).

In this paper, we have also stressed some ethical implications regarding Big Data, such as privacy and confidentiality, that demand a new approach in protecting the privacy and informed consent of the individual. Vaccinology and Big Data raise the question of which countries of individuals will have the opportunity to benefit from new omics technologies. We can conclude that Big Data in vaccinology bring us more benefits. We have to take advantage of Big Data in vaccinology with the incorporation of ethical standards by guaranteeing the global use of beneficial fruits of Big Data in vaccinology and protecting the old foundations of ethics, such as privacy, confidentiality, and informed consent.

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Mjesto golemih podataka (*Big Data*) u rješavanju sve većih problema vakcinologije u 21. stoljeću

SAŽETAK

Cijepljenje se danas, kao veliko dostignuće javnog zdravstva dvadesetog stoljeća, suočava s dvojbama, pitanjima i sumnjama koje se mogu povezati s pojmom neodlučnosti odnosno nesigurnosti. Vakcinologiju 21. stoljeća obilježava porast protuvakcinalnih pokreta koji su popraćeni odgovorima stručnjaka s različitih aspekata u cilju rješenja i odgovora. Globalizacija u zdravstvu s jedne strane, kao i velika tehnološka postignuća s druge strane, stvaraju okolnosti u kojima je enormna količina podataka javno dostupna. Stručnjaci temelje dobrobit cijepljenja na znanstvenim podatcima. Isto se tako i roditelji, koji su neodlučni po pitanju cijepljenja, kao i protivnici cijepljenja, također pozivaju na činjenicu da svoje stavove temelje na znanstvenim činjenicama. Pedijatri u primarnoj praksi prvi su koji se susreću s roditeljima koji su neodlični po pitanju cijepljenja, a sve više svjedoče nemogućnostima da im se suprotstave, kao i nemogućnostima drugih stručnjaka koji su uključeni u cijepljenje. U okolnostima u kojima postoji enormna količina podataka lako je izvući jedan određeni i interpretirati ga na različite načine. Jasno je kako stari način „obrane“ položaja cjepiva kao jednog od velikih postignuća 20. stoljeća nije više primjeren. S druge strane, istraživanje literature ukazuje da pojam golemi podatci (*Big Data*) naveliko ulazi u medicinu općenito kao i u područje javnog zdravstva i cijepljenja. Ovaj rad ima za cilj, temeljem istraživanja literature i stavova autora, pozicionirati ulogu golemih podataka, *Big Data,* (dobrobiti, zamke, etičke implikacije) u cijepljenju 21. stoljeća.

Ključne riječi: cijepljenje, golemi podatci, etika golemih podataka