Drug Saf (2018) 41:541–543
https://doi.org/10.1007/s40264-018-0655-1

LETTER TO THE EDITOR

Authors' reply: Safety of Human Papillomavirus Vaccines

Kristine Macartney[1,2] · Anastasia Phillips[1] · Cyra Patel[2] · Alexis Pillsbury[2] · Julia Brotherton[3,4]

Published online: 26 March 2018

We strongly disagree with the assertions made by Chandler et al. [1] and Martinez-Lavin [2] regarding our use of evidence [3] and with the validity of the alternative information presented by the authors.

Chandler et al. [1] contend that a hierarchy of evidence is outdated and that we use epidemiological evidence to "trump" the findings of case reports and case series. The evidence hierarchy used to structure our review is a globally accepted paradigm in modern clinical medicine and healthcare [4]. Modifications to this hierarchy routinely place case series and case reports as the lowest level of evidence [5], reflecting their high risk of bias. We note that both Chandler et al. [1] and Martinez-Lavin [2] cite multiple very small and largely observational studies with no controls, several of which have been criticized [6, 7]. This is despite Martinez-Lavin [2] questioning the validity of "small" clinical trials.

This reply refers to the articles available at https://doi.org/10.1007/s40264-018-0656-0 and https://doi.org/10.1007/s40264-018-0657-z.

✉ Kristine Macartney
Kristine.Macartney@health.nsw.gov

[1] The University of Sydney, Sydney, NSW, Australia

[2] National Centre for Immunisation Research and Surveillance, Kids Research Institute, The Sydney Children's Hospitals Network, Cnr Hawkesbury Road and Hainsworth Street, Westmead 2145, NSW, Australia

[3] National HPV Vaccination Program Register, Victorian Cytology Service, Level 6, 176 Wellington Parade, East Melbourne, VIC 3002, Australia

[4] The University of Melbourne, Melbourne, VIC, Australia

The vast majority of evidence-based reviews on any topic do not include case series or case reports at all because of their inherent biases. In our review, we included such reports and acknowledged that they can have a role in raising potential safety issues; we did not characterize them as "anecdotes" or "coincidence," as suggested by Chandler et al. [1]. Case reports allow patients and physicians to raise concerns and may contribute to hypothesis generation [3]. This has been recognized for decades and has underpinned the development of specialist adverse events clinics and networks in some countries which not only provide assessment and support for those who have experienced an adverse event but also facilitate systematic gathering of data to investigate concerns [8–11]. In the case of human papillomavirus (HPV) vaccines, this has occurred. As described in our two reviews [3, 12], in addition to an extensive body of clinical trial evidence demonstrating the safety of HPV vaccines, dozens of robust well-designed studies to investigate specific concerns have been conducted.

Chandler et al. [1] discuss variability in immunological responses to vaccination and appear to contend that case reports present data on individuals of "unusual susceptibility" to adverse events too rare to detect in epidemiological studies [1]. Yet, the opposite is true. Well-designed epidemiologic studies have, at their center, carefully validated case definitions, such as those published for potential adverse events by multi-disciplinary experts from the Brighton Collaboration. Martinez-Lavin [2] cites publications, including Chandler et al. [13], that describe symptoms such as headache, fatigue, dizziness, and musculoskeletal pain at highly variable times post-

vaccination. These are common concerns; their occurrence does not imply they are caused by vaccination. In contrast, well-designed population-based studies have been used to investigate signals for, and determine the post-vaccination risk of, clearly defined and validated adverse events, including Guillain-Barré syndrome following influenza vaccination [14], narcolepsy following adjuvanted pandemic influenza vaccine [15], thrombocytopenia following the measles, mumps, and rubella (MMR) vaccine [16], and anaphylaxis following numerous individual vaccines [17].

With regard to the new era of "predictive vaccinology" discussed at length by Chandler et al. [1], we agree future developments in this field will undoubtedly help us to better understand observed individual variation in immunogenicity, efficacy, and reactogenicity to vaccines. However, the inference, if intended, that further developments in this field give validity to unsupported assumptions of causal relationships between vaccination and adverse events based on temporal associations alone is dangerous. There is potential, over the coming decades, for immunogenomics and systems biology approaches to study vaccine effects and perhaps, in years to come, provide the ability to identify predictive biomarkers for different outcomes [18, 19]. Yet even then, practical applications would need careful consideration [18]. Vaccines routinely recommended at a population level are currently held to the highest possible standards with respect to safety and overall benefit:risk profile, underpinned by extensive high-quality evidence as detailed in our and others' reviews of HPV vaccines [3].

Martinez-Lavin [2] also presents an analysis of clinical trial data from a previously published letter [20] that has been criticized by others [21]. The additional ad hoc analyses presented are flawed and do not account for a lack of temporal association [22], with no clear methodology provided for the calculation of number needed to vaccinate. Overwhelmingly, our and other quality reviews have demonstrated the safety of HPV vaccination and a positive benefit:risk profile. Regarding some of the other conditions cited in his letter, as stated in our paper [3], the European Medicines Agency (EMA) [23] and the World Health Organization's Global Advisory Committee on Vaccine Safety [24] also concluded there was no evidence of an association between HPV vaccine and postural orthostatic tachycardia syndrome or complex regional pain syndrome; the EMA reviewed the work by Martinez-Lavin [21] for their report.

HPV vaccines are highly effective in reducing HPV infections, genital warts, and pre-cancerous lesions of the cervix [25, 26]; reductions in cervical cancers are expected to occur imminently in vaccinated populations. As evidenced in our review [3], and that of other independent groups [23, 24, 27, 28], robust scientific evidence from around the globe supports the safety of these vaccines.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this study.

Conflicts of interest Kristine Macartney, Anastasia Phillips, Alexis Pillsbury and Cyra Patel have no conflicts of interest that are directly relevant to the content of this study. Julia Brotherton is employed as the Director of the National HPV Vaccination Program Register, which is owned and funded by the Australian Government Department of Health. She has been an investigator on investigator-initiated HPV epidemiology studies that have received unrestricted partial funding for laboratory components from Seqirus (cervical cancer typing study) and Merck (recurrent respiratory papillomatosis study) but has never received any personal financial benefits.

References

1. Chandler RE, Edwards IR, Lindquist M. Comment on "Safety of human papillomavirus vaccines: an updated review". Drug Saf. 2018. https://doi.org/10.1007/s40264-018-0657-z.
2. Martinez-Lavin M. Comment on: "Safety of Human Papillomavirus Vaccines: An Updated Review". Drug Saf. 2018. https://doi.org/10.1007/s40264-018-0656-0.
3. Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K. Safety of human papillomavirus vaccines: an updated review. Drug Saf. 2017;41(4). https://doi.org/10.1007/s40264-017-0625-z.
4. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336(7651):995–8.
5. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evid Based Med. 2016;21(4):125–7.
6. Hanley S, Pollock K, Cuschieri K. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine [letter]. Intern Med (Tokyo, Japan). 2015;54(15):1953.
7. Petousis-Harris H. Proposed HPV vaccination syndrome is unsubstantiated [letter]. Clin Rheumatol. 2015;35(3):833–4.
8. Crawford NW, Hodgson K, Gold M, Buttery J, Wood N. Adverse events following HPV immunization in Australia: establishment of a clinical network. Hum Vaccin Immunother. 2016;12(10):2662–5.
9. LaRussa PS, Edwards KM, Dekker CL, Klein NP, Halsey NA, Marchant C, et al. Understanding the role of human variation in vaccine adverse events: the clinical immunization safety assessment network. Pediatrics. 2011;127(Suppl 1):S65–73.
10. Williams SE, Klein NP, Halsey N, Dekker CL, Baxter RP, Marchant CD, et al. Overview of the clinical consult case review of adverse events following immunization: clinical immunization safety assessment (CISA) network 2004–2009. Vaccine. 2011;29(40):6920–7.
11. Top KA, Zafack J, De Serres G, Halperin Serres G. SA, for the PI. Canadian paediatricians' approaches to managing patients with adverse events following immunization: The role of the Special Immunization Clinic network. Paediatr Child Health. 2014;19(6):310–4.
12. Macartney K, Chiu C, Georgousakis M, Brotherton J. Safety of human papillomavirus vaccines: a review. Drug Saf. 2013;36(6):393–412.

13. Chandler R, Juhlin K, Fransson J, Caster O, Edwards I, Norén G. Current safety concerns with human papillomavirus vaccine: a cluster analysis of reports in VigiBase®. Drug Saf. 2017;40(1):81–90.
14. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol. 1979;110(2):105–23.
15. Sarkanen TO, Alakuijala APE, Dauvilliers YA. Partinen MM. Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis. Sleep Med Rev. 2018;38:177–86. https://doi.org/10.1016/j.smrv.2017.06.006.
16. Miller E, Waight P, Farrington C, Andrews N, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine. Arch Dis Child. 2001;84(3):227–9.
17. Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, et al. Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics. 2003;112(4):815–20.
18. Poland GA, Ovsyannikova IG, Kennedy RB. Personalized vaccinology: A review. Vaccine. 2017. https://doi.org/10.1016/j.vaccine.2017.07.062.
19. Whitaker JA, Ovsyannikova IG, Poland GA. Adversomics: a new paradigm for vaccine safety and design. Expert Rev Vaccines. 2015;14(7):935–47.
20. Martinez-Lavin M. Vaccine-related serious adverse events might have been under-recognized in the pivotal HPV vaccine randomized trial. Clin Rheumatol. 2017;36(4):975.
21. Hawkes D. Response to "Vaccine-related serious adverse events might have been under-recognized in the pivotal HPV vaccine randomized trial". Clin Rheumatol. 2017;36(7):1691–2.
22. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmeron J. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet. 2014;384(9961):2213–27.
23. European Medicines Agency. Assessment Report: Review under Article 20 of Regulation (EC) No 726/2004, Human papillomavirus (HPV) vaccines. London: European Medicines Agency; 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500197129.pdf. [cited February 2018].
24. World Health Organisation. Meeting of the Global Advisory Committee on Vaccine Safety, 7–8 June 2017. Wkly Epidemiol Rec. 2017;92(28):393–404.
25. Brotherton JML, Bloem PN. Population-based HPV vaccination programmes are safe and effective: 2017 update and the impetus for achieving better global coverage. Best Pract Res Clin Obstet Gynaecol. 2018;47:42–58.
26. Drolet M, Benard E, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis. 2015;15(5):565–80.
27. Gee J, Weinbaum C, Sukumaran L, Markowitz LE. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. Hum Vaccin Immunother. 2016;12(6):1406–17.
28. Vichnin M, Bonanni P, Klein NP, Garland SM, Block SL, Kjaer SK, et al. An overview of quadrivalent human papillomavirus vaccine safety: 2006–2015. Pediatr Infect Dis J. 2015;34(9):983–91.