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On the contextual nature of vaccine safety monitoring: Adverse events reporting after HPV-vaccination in Denmark, 2015

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Background: In 2013-15, Denmark experienced an increase in reported suspected adverse events following vaccination (AEFI) against human papilloma virus (HPV). Dedicated centres ("One Access") were established in order to standardize management of patients who experienced medically unexplained physical symptoms after HPV vaccination. Since One Access was targeted patients with suspected AEFI after HPV vaccination, we used this opportunity to estimate completeness in AEFI reporting to the Danish Medicines Agency (DMA), and explore the topic of AEFI reporting from the perspective of physicians working at the centres to better understand health professionals' reporting behaviour.

Methods: The study consisted of a quantitative and a qualitative part. In the quantitative analysis, we used the Danish civil registry number to merge a line-list of all One Access patients referred in 2015 with total number of patients who had reported suspected serious AEFI following HPV vaccination to the DMA in the years 2009-2015. We conducted four semi-structured interviews with doctors representing three out of five regions. The Theoretical Domains Framework together with empirical data from two clinical fieldtrips guided the formation of the qualitative study.

Results: Among 1577 One Access patients, only 404 (26 %) were reported to the DMA. We found significant regional differences in reporting completeness ($p < 0.001$) and differences between regions when looking at reporters' backgrounds (healthcare professionals vs non-professionals; $p = 0.004$). We identified several factors of importance for reporting behaviour amongst physicians, mainly under the domains of Knowledge, Motivation & Goals, and Environmental Context.

Conclusions: Despite an official aim of homogenous case management, reporting of suspected AEFI was incomplete with large regional differences. The qualitative study corroborated that reporting behaviour was contextual. This observation represents an important caveat in interpreting data from AEFI reporting, in particular when these data are used for research or policymaking.

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Keywords: adverse events following vaccination; HPV vaccine; vaccine safety monitoring; passive surveillance systems; human papilloma virus.

Introduction

After a vaccine has been approved and distributed on the market, national authorities continue to monitor its safety. Systems for reporting of adverse events following immunization (AEFI) constitute one of the tools to pick up safety signals post-licensure of vaccines. The systems are passive, which means that information is provided by individuals (health care providers, patients, relatives, lawyers, etc.) who voluntarily report their experience. Therefore, passive surveillance of AEFI depends on the intuition, beliefs, context, and many other factors of the individuals who report (1). The data are subject to bias, including underreporting, as well as stimulated reporting, which is elevated reporting that may occur in response to media attention or increased public awareness (1). Because there is no "gold standard" for reporting AEFI, determinants for reporting of AEFI are difficult to evaluate. The formation of a Danish national network of clinics to assist patients with suspected AEFI after vaccination against human papilloma virus (HPV) provided an opportunity to examine reporting behaviour.

The HPV vaccine was introduced in the Danish children's vaccination programme in 2009 and was initially well-received. From 2013 Denmark saw a significant rise in reported AEFI from 95 cases in 2012 to 511 cases in 2013, reaching an all-time high of 820 cases in 2015 (2). Common symptoms included among others headache, orthostatic intolerance, fatigue, nausea, cognitive dysfunctions and disordered sleep (3-5). The patients were additionally characterized by increased health care seeking behaviour before the initiation of the HPV immunization series (6,7) and an average lower socioeconomic status than a reference population (8). The increase in reports of AEFI was stimulated by intensive media attention and was followed by a considerable drop in vaccine uptake (9,10).

In the summer of 2015, in a politically motivated attempt to improve and standardize management of patients with suspected AEFI from the HPV vaccine, diagnosis and treatment was organised in one national network – termed *One Access* (11). The network comprised nine clinical hospital departments in the five Danish regions. Patients eligible for One Access should have a history of HPV vaccination and suspected AEFI, and be referred by their general practitioner or a hospital as part of the diagnostic process.

In the present paper we used quantitative and qualitative methods to explore reporting of AEFI.

The aim of the study was to better understand the process of AEFI reporting from the perspective of the health professionals. This is of obvious interest because AEFI reporting remains a cornerstone in vaccine safety monitoring and because the data are used for risk assessment and policymaking.

Methods

Quantitative study:

We obtained data from the passive notifications of AEFI from the HPV vaccine reported to the DMA between 2009 and 2015. Furthermore, we collected data from each One Access clinic in the form of a simple line-list of patients referred to One Access in 2015. The Danish Civil Registry System number (CRS), which is a unique personal identifier that identifies all persons with residence in Denmark, was included in both datasets, and the two datasets were merged with this this unique number as key.

The DMA database consisted of 776 patients with reported serious adverse events to the HPV vaccine between 2009 to 2015. Data included their unique CRS number, as described above, as well as the professional background of the reporter for each reported AEFI; date of symptom onset; and the date the AEFI report was registered with the DMA. The dataset from the One Access clinics included 1606 patients with their CRS number and which region they had been referred to for treatment. After deleting 29 duplicates (referred to more than one region), the line-list from One Access comprised 1577 patients.

We determined completeness of reporting by region and differences in who filed the report to the DMA. We analysed the data by contingency table analysis using Chi-square with a p-value of 5 % as level of significance. All analyses were carried out in Stata 14.2 (StataCorp, College Station, Texas).

Qualitative study:

We conducted individual, face-to-face, semi-structured interviews in the period of October-November 2017. We selected key informants working at One Access from three of the five regions for interviews. Selection was based on extreme case sampling by including participants from the region with the highest (Region A) and the lowest (Region D) reporting percentage. This was based on the assumption that the different reporting percentages reflect different reporting practices between the regions. We also included participants from a region with reporting rates somewhere in the middle of the two (Region B) to provide better opportunities to contrast and compare the findings. One Access was run by between three and nine doctors in each region, except for one region in which services to adults were shared by 18 different physicians. In total, 44 doctors from the nine different departments contributed to One Access, albeit with different hours of work. Each department had one or two key physicians who coordinated and managed the patients. The participants for our study were selected from this latter group who saw most of the patients. We conducted four interviews in total including one participant from Region A, one from Region B, and two from Region D. The semi-structured interviews lasted between 40-60 minutes each.

The Theoretical Domains Framework

We adapted the Theoretical Domains Framework (TDF) to inform the interview guide and interpret the data (12-15). The TDF is a theoretical framework designed to identify barriers and facilitators to the implementation of evidence-based practices. It includes 12 domains with particular importance for behaviour and behaviour change in health care settings. In the present study, the behaviour in question is reporting of suspected AEFI following HPV vaccination. Although there is no “gold standard” in passive reporting of AEFI, the TDF represents a useful framework due to its broad theoretical scope and, thus, its potential to generate theory-based information on factors influencing behaviour in health care settings.

In addition to application of the domains from the TDF, we carried out fieldwork conducting participant observation and informal interviewing at two regional One Access clinics prior to the interviews (16). The purpose of the fieldtrips was to inform the interview guide and contextualize the findings. They lasted 4-5 hours each and focused on the set-up at the clinics and the

interaction between physicians and patients. This allowed for a mix of theory and empirical data to inform the design of the interview guide.

Analysis

All interviews were audio recorded and verbatim transcribed. The subsequent analysis was based on two rounds of coding: first, data-driven inductive coding, allowing for empirical exploration of themes that may fall outside the TDF. In the second round, we took a deductive approach and coded the material directed by the TDF. We then contrasted and compared the themes identified from the two rounds of coding in the final analysis.

Privacy protection

Quantitative data: The study was included in the notification to the Danish Data Protection Agency under the record numbers 2008-54-0474 and 2015-57-0002.

Qualitative data: All participants were informed of the background and goal of the study and gave their informed consent to publish the data obtained from the semi-structured interviews in anonymous form.

Results

Quantitative study

Among the 1606 patients who had been seen at One Access, 29 were duplicates (i.e., being seen in more than one region). Duplicates were deleted by date (including the first referral in the study). All in all, 404 (25.6 %) of the remaining 1577 One Access patients referred in 2015 were reported to the DMA, Table 1.

Between the regions, we found significant differences in the completeness of reporting, ranging from only 14.2 % of the patients being reported to the DMA in region D to 35.4 % in region A, $p < 0.001$, Table 1. Thus, the likelihood of reporting suspected AEFI from the HPV vaccine varied across

regions, with Region A having the highest reporting percentage amongst their One Access patients.

Table 2 shows that there were significant regional differences in terms of *who* reported the suspected AEFI. Region A had the highest percentage of patients reported by a health care professional (79.3 %) whereas region C and D had only 54.1 % and 57.9 % of the reports from a health care professional. Further analysis between the regions with regards to reporter qualification (health care vs non-health care professional) revealed no statistically significant differences between Region A vs Region B ($p = 0.264$) or Region A vs Region E ($p = 0.071$), but showed statistically significant differences between Region A vs Region C ($p = 0.005$), as well as Region A vs Region D ($p = 0.001$). In other words, One Access doctors from Region A reported a statistically significantly higher percentage of their patients to the DMA than their colleagues in Region C or Region D.

Qualitative study

In the analysis we identified three main themes that may affect doctors' reporting practices. These are presented according to their domain in the TDF: 1) Knowledge, 2) Motivation & Goals, and 3) Environmental Context & Resources. We further included the domain Memory, Attention & Decision Process, as most participants expressed AEFI reporting as a *conscious choice*. Therefore, lack of memory or attention does not seem to explain reporting behaviour in our study.
Below we present a short summary of the four themes. Table 3 and 4 summarize the findings with illustrative examples.

Knowledge: Diffuse symptoms with no clear picture

We applied the Knowledge domain in a broader sense than in the original framework as including 1) participants' procedural knowledge, 2) the source of knowledge (information available from medical histories), 3) their knowledge about the patients' symptoms, and 4) their beliefs about the HPV vaccine and its relation to their patients' symptoms. Three of the four participants found that temporal relations between vaccine and symptoms were commonly either difficult to establish or missing. Another issue brought up in the interviews was the diffuse nature of the symptoms. Half

of participants found that the medical assessment of the symptoms as possible AEFI was complicated by the broad and unspecific symptom picture. Finally, we found a difference between participants' beliefs about the origin of the symptoms: one participant focused mainly on a biomedical explanation including overstimulation of the autonomous nervous system – a mechanism the participant explained may or may not be related to HPV vaccination. Remaining participants explained that they had seen numerous patients with these types of symptoms long before the HPV vaccine, and/or found other factors to be more likely explanations, especially psychological and social factors. The reporting rate reflected these beliefs. Participants from the latter group came from regions with lower reporting rate, whereas the participant who had a preunderstanding of a potential biomedical link between vaccine and symptoms came from one of the regions with the highest reporting completeness. Thus, factors belonging to the Knowledge domain appeared to influence participants' reporting behaviour in different directions depending on their previous experiences and their ideas about a possible causal relationship between the HPV vaccine and the symptoms experienced by their patients.

We found that participants from the regions with the highest reporting rates were more likely to have a low threshold for reporting and reported all cases in which they could not directly exclude that HPV vaccination caused their patients' symptoms. In contrast, participants from the region with the lowest reporting rate either said they would report only if they suspected the HPV vaccine potentially might have caused their patients' symptoms, or instead encouraged consumer reporting due to instructions from management level.

Motivation and goals: Reporting of adverse events serves an important purpose

All participants believed reporting of AEFI served an important, meaningful purpose and expressed that they were motivated to report suspected cases. Two participants mentioned centralized data collection of patients' symptoms as one of the main goals of the One Access initiative. They emphasized that a central agency such as the DMA would need to have all relevant data to be able to determine any epidemiological warning signs. This objective was described as so important that one participant explained he had a lower threshold for reporting in the setting of One Access than

he would usually have; he reported all cases where he could not directly exclude a possible correlation even if he didn't suspect the symptoms to be vaccine-related.

Although all participants were motivated for AEFI reporting in general, it seems that having the specific goal of centralized data collection in the context of One Access facilitated reporting. We noted, in this domain, that the qualitative and quantitative findings were in agreement. Participants who mentioned the goal of centralized data collection came from Region A and Region B (with high reporting percentage), as opposed to participants from Region D (low reporting percentage) who did not explicitly mention this as a main objective of One Access itself.

Environmental context and resources: Difficult to find the time to report all symptoms

Perhaps unsurprisingly, environmental context and resources were found to influence participants' reporting behaviour differently, as they each worked in different organizational environments. Two participants said time constraints or limited resources had not restricted their reporting. One participant explained he had been forced to report fewer cases in 2016 as a direct result of time constraints and lack of resources at the department, even though he was highly motivated for reporting. This behaviour is not reflected in our results as we only included data from 2015, but the example illustrates how time constraints can lead to behaviour change (and thus be a barrier to AEFI reporting). The last participant explained how the management at her department had decided to encourage consumer reporting of suspected AEFI rather than doctors making the reports.

Both participants from regions with higher reporting rates said they were busy but had sufficient time to report (although one participant changed his reporting behaviour to fewer reported cases in 2016 due to time constraints). Of the two participants from regions with lower reporting rates, one said time was not an issue for reporting of potential AEFI, whereas one came from the department where management had to decided to educate patients in online reporting – a decision the participant assumed was a means to save time in a busy clinical setting. Thus, it seems that sufficient time is a prerequisite for reporting of AEFI, but not a facilitating factor on its own.

Memory, attention, and decision process: Reporting is a conscious choice

All participants expressed that they were very aware of the importance of reporting AEFI and agreed it was not something they usually forgot. It was expressed as part of the job to assess whether or not symptoms could be suspected AEFI and therefore reported to the DMA. Thus, the behaviour of reporting was presented as a conscious choice – with the exception of one participant from the department where it had been decided at management level not to report but instead educate patients in online consumer reporting.

Discussion

Main results

We have organized the discussion of the main results in two sections entitled 'Data from passive surveillance systems are context-dependent' and 'Factors influencing physicians' reporting behaviour'.

Data from passive surveillance systems are context-dependent

We found that data on AEFI from passive surveillance systems depend on the context in which they are gathered. By "context" we refer to the multitude of circumstances affecting how reporting of AEFI takes place. This includes the situation within which such data are collected, how the data are collected, who reported the data, and why they reported, as well as the institutional environment affecting the reporting situation together with the broader societal circumstances in which reporting takes places.

Denmark is a small and homogenous country with free and equal access to health care. One of the objectives of the establishment of One Access was to offer equal opportunities for management in case of suspected AEFI following HPV vaccination (11). Therefore, we expected reporting of AEFI to be similar across regions. However, we found significant regional differences in reporting rates. It seems unlikely that these differences reflect an actual regional variation in AEFI, but rather differences in reporting practices amongst physicians and patients in the regions. Additionally, we found significant differences between regions when looking at *who* reports the suspected AEFI

(healthcare professional vs non-professionals). We found that patients referred to region A were more likely to have had their symptoms reported by a healthcare professional (79.3 %). This region also had the highest completeness in reporting. This is in contrast to regions C and D where 57.9 % and 54.1 % of the reports were made by a healthcare professional. In the sections below, we discuss the key factors we have identified to influence reporting practices among the participants of this study.

Factors influencing physicians' reporting behaviour

Knowledge in its broadest sense

Identifying a temporal relation between the vaccine and symptoms was described as the most important factor when physicians assessed whether symptoms should be reported as suspected AEFI. Unclear or missing temporal relations, diffuse symptoms, and multiple symptoms appeared to complicate the decision process of reporting or not for some participants. Based on the limited number of interviews, we propose that participants can be categorized as either low threshold or high threshold reporters, with some doctors reporting all cases in which they could not directly exclude a link between the HPV vaccine and symptoms, while others only reported cases where they actively suspected the vaccine potentially caused the symptoms. The qualitative results corroborate the quantitative findings, in that participants who said they had a low threshold for reporting came from the regions with the highest percentage of reported patients.

The significance of health care professionals' knowledge and ideas on AEFI reporting has been documented in other studies (17,18). Especially the challenge of assessing whether a given symptom could represent an adverse event or not has been identified as a barrier to AEFI reporting, with as many as 61% of participants in one study citing 'unclear definitions of a reportable AEFI' as a barrier to reporting (19). Unlike other studies (18,19), all of our participants reported good procedural knowledge of how to report, and good knowledge of the national reporting system itself. This indicates that technical skills and system knowledge on its own may not be sufficient to streamline AEFI data from passive surveillance systems. A better

295 understanding of high and low threshold reporting and how this may be compensated thus
296 constitutes an important question for further research.
297
298 *Data collection was "part of the job"*
299
300 Lack of motivation and purpose has been identified in multiple studies as a barrier to reporting of
301 AEFI and medical errors (20-22). All participants, including those who reported very few cases,
302 described high motivation for reporting adverse events in general. However, some participants
303 explicitly expressed that reporting of suspected AEFI was one of the *main objectives* of One Access
304 – as one physician explained, it was "part of the job" to gather information centrally. Participants
305 who reported few or no cases did not mention this data collection as a perceived goal of One
306 Access. On this basis, we suggest that a discrepancy in understanding of the core objectives of One
307 Access itself may contribute to different reporting practices amongst physicians, despite all
308 participants expressed a motivation for reporting of AEFI in general.
309
310 **Strengths and weaknesses**
311
312 Strengths
313
314 The strengths of this study include the use of both quantitative and qualitative methods. Data
315 from the semi-structured interviews allow for a deeper understanding of reporting behaviour
316 among physicians and enabled us to suggest important factors that may help explain the statistical
317 discrepancies observed between the regions in AEFI reporting. Thus, the qualitative data may
318 increase the usefulness of the quantitative findings, in that they help identify facilitators and
319 barriers to reporting that might be addressed to avoid either underreporting or stimulated
320 reporting of AEFI.
321
322 In addition, the individually unique CRS number which all patients are registered with both at One
323 Access and at the DMA allows for a complete merge between the two groups, making it possible
324 to examine the completeness of AEFI reporting in the context of HPV vaccination in Denmark.

Limitations

Quantitative

The DMA data included patients who have been classified with *'serious'* adverse events. It is possible that some patients have been referred to One Access with non-serious suspected AEFI, according to the DMA's classifications. However, it seems highly implausible that this would be the full explanation for the observed regional discrepancies, as most participants stated that the patients had symptoms that they would classify as serious, such as having caused hospitalization or extended periods away from school. As such, if they were reported, they would most likely be classified as serious suspected AEFI by the DMA.

Furthermore, by excluding DMA reports from 2016, we will likely have missed some patients referred in the last months of 2015 who have been reported to the DMA in 2016 – thus being misclassified as unreported cases in our study. Finally, as we included DMA data from 2009-2015, some patients may have moved to another region before the establishment of One Access and thus have been reported in a different region than that which we have connected them to in this analysis.

Qualitative

Traditionally, sample size in qualitative research is considered sufficient when theoretical saturation has been reached, that is, when no new information appears with new interviews (23). However, as Malterud et al. point out, sample size should also be guided by the aim of the study (23). The aim of the present study was to explore possible explanations for differences in reporting practices. The total number of interviews conducted is small (four interviews), and it is likely that information from further interviews would have contributed with additional insights. Nonetheless, our material demonstrates important differences in reporting practices, and provides insight into the quantitative findings. While we cannot claim saturation, we found a pattern in responses, and have identified key factors that appear to affect reporting practices amongst physicians working at One Access which are supported by the quantitative findings. To gain a more thorough understanding, this should be explored in future studies. However, it is noteworthy that our

qualitative findings of highly differing opinions and reporting practices is supported by our quantitative results, in which we have found statistically significant differences in reporting completeness and also in percentages of reports by healthcare professionals vs non-professionals, indicating different reporting behaviours amongst healthcare professionals between the regions. Though our findings may not be exhaustive, we have identified important differences which affect reporting practices amongst doctors from One Access, and the quantitative findings suggest that such differences exist at the regional level as well.

Implications for policymakers and researchers

When analysing and interpreting data from passive surveillance system, one must keep in mind the context in which the data are collected. Particularly in the case of AEFI in Denmark, it is noteworthy that One Access patients constitute a different population than the patients registered with the DMA: only 25.6 % of One Access patients are registered with the DMA as serious AEFI in 2015. Thus, 74.4 % of One Access patients referred in 2015 are unreported, receiving care for symptoms which in the context of One Access have inevitably been linked to HPV vaccination.

Additionally, our findings suggest that in order to increase reliability of AEFI data from passive surveillance systems, it would be helpful to attempt to streamline reporters' knowledge and ideas about what and when to report; for reporters to have similar goals and motivation for reporting; and, ideally, for reporters to have sufficient time to report AEFI.

Future studies

Future studies on the topic could 1) include larger sample sizes and determine facilitators and barriers of AEFI reporting using the TDF or similar frameworks, to further explore which factors are important to AEFI reporting and test the validity of our findings; 2) explore a possible hierachy between the domains in the TDF – i.e. are some domains more dominant or important than others in the context of AEFI reporting? In our study, we saw an example in which a participant motivated for AEFI reporting had decreased his reporting activity due to time constraints, perhaps suggesting

that *Environmental Context* may be a more dominant domain than *Motivation & Goals.* Finally, 3) we propose to develop interventions or guidelines to streamline reporting practices.

Conclusion

Reporting of suspected AEFI was incomplete with only 26 % cases seen at a dedicated referral system reported to the regulatory authority. In spite of an official aim of homogenous case management, there were great regional differences in reporting practices. The qualitative study corroborated that reporting behaviour was contextual, and that the factors influencing reporting behaviour were complex and dynamic. The physicians' experience and preunderstanding about symptoms and causality, available information from medical histories, time and resources, as well as differences in the understanding of the objectives of One Access were identified as influential factors in the process of reporting or not reporting. These issues should be kept in mind in order to increase reliability of information from passive surveillance systems.

The results from the present study represents an important caveat in interpreting data from AEFI reporting, in particular when these data are used for research, e.g., as done by the Uppsala Monitoring Centre (24) or policymaking.

Conflict of interest

The authors of this study have no conflicts of interest to declare.

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Table 1. Completeness in reporting of suspected Adverse Events following HPV vaccination, Denmark, 2015

Region	Patients seen in "One Access" with suspected AE after HPV-vaccination	Patients reported to the Danish Medicines Agency (DMA)	Reporting completeness (percent)
A	574	203	35.4%
B	280	70	25.0%
C	185	38	20.5%
D	261	37	14.2%
E	277	56	20.2%
TOTAL	**1577***	**404**	**25.6%**

$Chi^2(8) = 53.3543$ with $p < 0.001$

*29 patients seen in > 1 region were excluded

Table 2. Number of patients reported by a healthcare professional

Region	Healthcare – Yes	Healthcare – No	Total number of reported patients
A	161 (79.3%)	42 (20.7%)	203
B	51 (72.9%)	19 (27.1%)	70
C	22 (57.9%)	16 (42.1%)	38
D	20 (54.1%)	17 (45.9%)	37
E	37 (67.9%)	19 (32.1%)	56
Total	292 (72.3%)	112 (27.7%)	404

$Chi^2(4) = 15.6242$ with $p = 0.004$

Table 3. Participants' reasons for reporting

Reasons for reporting	Domain	Quote
One of the main goals of One Access was to gather information centrally on the patient group	Motivation & Goals	*"The centres were established to gather information on this group of patients with suspected adverse events..."*
Criteria for reporting are met	Knowledge	"*There are some very clear critera* [for reporting] *[…] most of them* [the patients] *meet the criteria for serious adverse events, and they should be reported. And we have reported a lot."*
Three year deadline for reporting	Environmental context	**"***They have to report their symptoms within three years[…] So it's a good idea to report, even if you don't have a solid foundation for the report."*
A causal relationship between HPV vaccine and symptoms cannot be excluded, and this link should be explored by the DMA	Knowledge/Motivation & Goals	*"I can't really see how you should be able to exclude a causal connection with absolute certainty. That's the DMA's job."*

Table 4. Participants' reasons for not reporting

Reasons for not reporting	Domain	Quote
The temporal relation is unclear or missing	Knowledge	*"[…] with no clear correlation, I think it's very difficult to know what to report."*
The symptoms are very diffuse	Knowledge	*"[...] this has been fairly diffuse symptoms with no clear picture, so I think it has been difficult to report."*
The clinical picture doesn't fit (no suspicion of relation to vaccine)	Knowledge	*"Situations like that were common, where things just didn't really add up."*
It's time-consuming	Environmental context	*"I simply haven't been able to report adverse events on top of everything else."*
Management decisions	Environmental context	*"I think that's probably why – for practical reasons – it's been decided that patients themselves should do the reporting."*