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Communication on Safety of Medicines in Europe

de Vries, Sietske; van der Sar, Maartje J. M.; Cupelli, Amelia; Baldelli, Ilaria; Coleman, Anna Marie; Montero, Dolores; Sipic, Ivana; Andric, Adriana; Wennberg, Annika; Ahlqvist-Rastad, Jane

Published in:
Drug Safety

DOI:
[10.1007/s40264-017-0535-0](https://doi.org/10.1007/s40264-017-0535-0)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

de Vries, S. T., van der Sar, M. J. M., Cupelli, A., Baldelli, I., Coleman, A. M., Montero, D., ... SCOPE Work Package 6 (2017). Communication on Safety of Medicines in Europe: Current Practices and General Practitioners' Awareness and Preferences. *Drug Safety*, 40(8), 729-742. DOI: 10.1007/s40264-017-0535-0

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Communication on Safety of Medicines in Europe: Current Practices and General Practitioners' Awareness and Preferences

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Published online: 24 May 2017

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Abstract

Introduction National competent authorities (NCAs) for medicines coordinate communication relating to the safety of medicines in Europe. The effectiveness of current communication practices has been questioned, particularly with regard to reaching general practitioners (GPs).

Objective The aim of this study was to assess current European NCA safety communication practices and to investigate European GPs' awareness of and preferences for safety communications on medicines.

Methods Web-based surveys were distributed among European NCAs and healthcare professionals (HCPs). The survey among regulators was emailed to a representative of

each of the 27 European countries participating in the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. HCPs from nine European countries (Denmark, Spain, Croatia, Ireland, Italy, The Netherlands, Norway, Sweden, and the UK) were asked about their preferences through a link to the survey on websites, in newsletters, and/or in a direct email. From this survey, data from GPs were used and descriptive analyses were conducted.

Results Current NCA practices were reported for 26 countries. In 23 countries (88%), NCAs published direct healthcare professional communications (DHPCs, i.e. urgent communication letters for serious safety issues) on their website in addition to distribution to individual HCPs. Educational materials were available on the NCA's website in 10 countries (40%), and 21 NCAs (81%) indicated they had their own bulletin/newsletter, which is often presented on the NCA's website (15 countries; 60%). More than 90% of the 1766 GPs who completed the survey were aware of DHPCs. The most preferred senders of safety information were NCAs and professional bodies, while the preferred channels for keeping up to date with safety information were medicines reference books and clinical guidelines. GPs found the repetition of safety issues useful (range of 80% in the UK to 97% in Italy). Preference for an electronic copy rather than a hardcopy varied per country (36% in Sweden to 72% in Spain).

Conclusions NCAs use similar methods for safety communications on medicines. Most GPs were aware of urgent communications and preferred similar senders of safety communications; however, their preferences towards the format differed per country.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-017-0535-0) contains supplementary material, which is available to authorized users.

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Key Points

Current safety communication practices are relatively similar among national competent authorities (NCAs).

Among European countries, there are differences in general practitioners' preferences towards the format (electronic versus hardcopy) of safety communications.

To improve safety communication strategies, it should be clear to the receiver that the information comes from the NCA or another preferred sender, such as a professional body.

1 Introduction

Important new drug safety issues need to be communicated to healthcare professionals (HCPs) to inform them and, if necessary, promote changes in their prescribing practices, to minimise patient harm and facilitate informed decision making [1]. In the EU, the Good Pharmacovigilance Practices module on safety communication (GVP XV) describes the strategies that can be used by national competent authorities (NCAs) and pharmaceutical companies for safety communications of new or emerging safety information [1]. The main tools are direct healthcare professional communications (DHPCs) and the NCAs own communications (e.g. newsletters). DHPCs are usually distributed by pharmaceutical companies following NCA approval of the content. Both communications are distributed to individual HCPs and/or are made available on the NCA's website. They contain important safety information and usually a recommendation on what action to take [1]. Safety messages may be strengthened by utilising other tools such as publications in scientific journals, newsletters of professional bodies, or, more recently, via e-communications, such as social media and mobile applications (apps). In certain situations, when a safety issue is complex or particularly serious, NCAs can decide that educational materials, directed to HCPs and patients, should be developed by a pharmaceutical company [2]. The key messages of such materials are agreed at European level by the European Medicines Agency (EMA) and the detailed text is reviewed by NCAs. The materials instruct patients how best to use a certain medicine and/or instruct HCPs what to consider when prescribing a certain medicine. They are usually presented as small booklets but can also be available electronically.

Awareness of these tools is mixed among various professions. A survey among HCPs conducted in The Netherlands showed that general practitioners (GPs) were less aware of DHPCs and less often visited the NCA's website than other HCPs. GPs also indicated that keeping themselves up to date on new drug safety issues took too much time [3]. Another survey, among European GPs and specialists, showed that only 37% of responders recalled the receipt of educational materials from a pharmaceutical company relating to a specific safety issue. Interestingly, this percentage varied across European countries, from 16% in Germany to almost 70% in Romania. Possible reasons for this variation could be the differences in the used distribution methods, differences in timing of the survey, and the different mix of responders across countries [4].

In general, NCAs may differ in their practices regarding communication of new safety issues to HCPs. Until now, there has been no overview of practices that are used by NCAs and to what extent these practices correspond with GPs' awareness of specific communications and their preferences for specific senders and channels, and the format and repetition. The current study aims to fill this gap in order to further improve the communication of safety issues to GPs by assessing (1) current European NCA risk communication practices, and (2) European GPs' awareness and preferences regarding safety communications.

2 Methods

For this descriptive study, data were extracted from three surveys conducted within the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) project (<http://www.scopejointaction.eu/>). This project, sponsored by the European Commission, aims to help NCAs fulfil the requirements of the pharmacovigilance legislation that came into practice in 2012. Part of this project, undertaken through Work Package 6, focused on risk communications. Web-based surveys were distributed to NCAs and HCPs.

2.1 Current Safety Communication Practices in National Competent Authorities (NCAs)

Two surveys aimed to identify the current safety communication practices of NCAs. In 2014, these surveys were sent to the NCAs of the 27 European countries participating in the SCOPE Joint Action, i.e. Belgium (BE), Bulgaria (BG), Croatia (HR), Cyprus (CY), Czech Republic (CZ), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Greece (GR), Hungary (HU), Iceland (IS), Ireland (IE), Italy (IT), Latvia (LV), Lithuania (LT), Malta (MT), The

Netherlands (NL), Norway (NO), Poland (PL), Portugal (PT), Romania (RO), Slovakia (SK), Slovenia (SI), Spain (ES), Sweden (SE), and the United Kingdom (UK). Both surveys were developed by the SCOPE Work Package 6 active partners.

One survey had a general focus on NCAs' methods of communication on safety of medicines, and contained questions about current practices related to DHPCs, NCA communications, and additional strategies to increase HCPs' awareness of safety issues that were relevant for this study (see electronic supplementary material 1a). The other survey focused on the use of web portals and contained questions about current practices related to the use of the NCA's website and on strategies to increase HCPs' awareness of safety information on the NCA's website (see electronic supplementary material 1b).

The web-based format of the surveys was constructed using SurveyMonkey (SurveyMonkey Inc., Palo Alto, CA, USA; <https://www.surveymonkey.com/>). A link to each of the surveys was sent by email to a contact person (i.e. a regulatory representative) in all NCAs participating in the SCOPE Joint Action. For both surveys, two reminder emails were sent. Answers were checked by the Work Package 6 active partners and corrected where necessary.

2.2 General Practitioners' Awareness and Preferences Regarding Safety Communication

A third survey, performed between June and September 2015, was distributed among HCPs in the nine European countries of which the NCA actively participated in Work Package 6 (i.e. DK, ES, HR, IE, IT, NL, NO, SE, and the UK). The aim of this survey was to assess HCPs' awareness and preferences regarding risk communication. GPs, pharmacists and cardiologists were the target population for this survey. For the current study, the GP data were used.

The survey was developed in English by the SCOPE Work Package 6 active partners, and contained questions about whether GPs had ever seen DHPCs, NCA communications and educational materials (awareness), as well as their general preferences towards the format, repetition, sender, and distribution channels (see electronic supplementary material 1c). Examples of DHPCs, NCA communications and educational materials that were recently distributed in participating countries were presented to responders from the respective countries to make clear what these materials entailed and what they were meant for. Preferences for various senders and channels were measured on a 5-point Likert scale ranging from very negative (1) to very positive (5). 'Senders' refer to persons/organisations that distribute the information (e.g. NCAs,

pharmaceutical companies, researchers, press), whereas 'channels' refer to strategies through which information is disseminated (e.g. personalised letter, email, social media). Where necessary, the questions were customised for each country to provide local information to responders or to remove irrelevant questions.

The English version of this survey was translated by an official translation agency into Danish, Spanish, Croatian, Italian, Dutch, Norwegian, and Swedish. Back-translation was performed by local SCOPE Work Package 6 members according to previously suggested methods [5], and changes were made if necessary. The final versions were entered into the Unipark software (<http://www.unipark.com/en/>). To minimise missing answers, a reminder appeared in the survey when a question was not completed.

The web-based surveys were checked by local SCOPE Work Package 6 members and pilot-tested by three to five people per country. After minor adaptations, the surveys were distributed through a link to the survey on websites, in newsletters, and/or in an email sent by the NCA, a professional body or a commercial organisation to their subscribers or members. To stimulate response rates, two countries (NL and the UK) organised a prize draw for responders to win a voucher (€50 and £50, respectively).

2.3 Analyses

Descriptive analyses were conducted and results presented for each country. For the GP data, numbers and percentages of the total included population were additionally calculated, as well as the mean of the country percentages, the latter to give equal weight to participating countries. For questions measured on a 5-point Likert scale, means and 99% confidence intervals (CIs) were calculated for the total group of responders and per country. The standard error was used in the 99% CIs [6]. Data on the current NCA safety communication practices were analysed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA), while data on GPs' awareness and preferences were analysed using Stata version 13 (StataCorp LLC, College Station, TX, USA).

3 Results

3.1 Current NCA Safety Communication Practices

Of the 27 regulatory representatives contacted, 26 and 25 representatives completed the survey relating to national methods of safety communications and the survey relating to web portals, respectively (Table 1). Responders from each country indicated that the NCA has its own website.

Table 1 Current (2014) risk communication practices

	BE	BG	CZ	DK	EE	ES	FI	FR	GR	HR	HU	IS	IE	IT	LV	LT	MT	NL	NO	PL	PT	RO	SE	SK	SI	UK	
DHPCs																											
-NCA allows companies to distribute DHPCs by email without sending a hard copy	-	-	+	-	+	+	+	+	-	-	-	-	-	-	+	+	+	-	-	+	+	+	-	-	-	-	
-DHPCs are published on the NCA's website	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	
-NCA disseminates DHPCs via electronic means in addition to distribution by companies	-	-	-	-	-	-	-	-	+	-	+	+	+	+	-	-	+	+	-	-	+	-	-	-	-		
-NCA uses patient organizations and professional bodies to distribute DHPCs	-	-	+	+	-	+	-	+	+	-	-	-	+	+	+	-	+	-	-	-	+	-	-	-	+		
NCA communications																											
-NCA publishes bulletin / safety newsletter	~	+	~	+	~	~	-	~	-	+	~	-	+	+	+	-	~	~	~	~	+	-	+	~	~	+	
-Bulletin/newsletter on NCA's website	+	+	+	+	-	-	-	+	-	-	+	-	+	+	+	-	+	-	+	?	+	-	+	+	-	+	
-NCA distributes bulletin via post to HCPs	-	+	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-	-	-	
-NCA distributes bulletin via email to HCPs	-	-	+	+	-	-	-	+	-	+	-	-	+	+	+	-	+	+	-	+	-	+	+	-	-	+	
-NCA distributes bulletin to HCPs indirectly via professional bodies using emails	-	-	-	-	-	-	-	+	-	+	-	-	+	+	-	-	+	-	-	-	-	-	-	-	-	-	
-NCA reproduces safety communications from EMA press releases on its website	+	+	+	~	~	-	~	+	~	+	-	+	+	+	~	+	~	~	~	+	+	+	~	~	+	~	
-NCA publishes own press releases	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	?	+	
-Direct contact with interest groups	~	~	~	~	-	-	~	~	-	~	~	~	~	~	~	-	~	~	~	-	~	+	~	~	~	+	
Educational materials																											
-Available on NCAs website	+	-	+	-	+	+	+	+	-	-	-	-	-	-	-	-	+	+	-	?	+	-	-	-	-	+	
-Link on NCA website to external webpage	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	?	-	-	-	-	+	

BE = Belgium, BG = Bulgaria (BG), CZ = Czech Republic, DK = Denmark, EE = Estonia, ES = Spain, FI = Finland, FR = France, GR = Greece, HR = Croatia, HU = Hungary, IS = Iceland, IE = Ireland, IT = Italy, LV = Latvia, LT = Lithuania, MT = Malta, NL = Netherlands, NO = Norway, PL = Poland, PT = Portugal, RO = Romania, SK = Slovakia, SI = Slovenia, UK = United Kingdom
 + Yes always / yes; ~ Yes, occasionally / Yes, on a case by case basis / Sometimes, depending on the topic; - No; ? Country did not complete web-portals survey / Missing
 NCA = National competent authority; DHPC; Direct Healthcare Professional Communication; HCP = Healthcare professional; EMA = European Medicines Agency

BE Belgium, BG Bulgaria, CZ Czech Republic, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GR Greece, HR Croatia, HU Hungary, IS Iceland, IE Ireland, IT Italy, LV Latvia, LT Lithuania, MT Malta, NL Netherlands, NO Norway, PL Poland, PT Portugal, RO Romania, SE Sweden, SK Slovakia, SI Slovenia, UK United Kingdom, NCA national competent authority, DHPC direct healthcare professional communication, HCPs healthcare professionals, EMA European Medicines Agency, + indicates yes always/yes, ~ indicates yes, occasionally/yes, on a case-by-case basis/sometimes, depending on the topic, - indicates no, ? indicates country did not complete the web-portals survey/missing

3.1.1 Direct Healthcare Professional Communications

In 11 countries (42%), pharmaceutical companies distributed DHPCs by email without additionally sending a hardcopy version (Table 1). In the remaining 15 countries, paper-based distribution is still compulsory. In addition, in most countries (23 of the 26; 88%), the NCA published DHPCs on their national website, provided these DHPCs had been previously approved by the NCA. In seven countries, the NCA disseminated DHPCs, at least sometimes, directly to (subscribed) HCPs via electronic means in addition to distribution of DHPCs by pharmaceutical companies. Moreover, NCAs sometimes used patient organisations and/or professional bodies (11 of the 26; 42%) to further distribute DHPCs. IE, LV, NL, and RO used all of these additional distribution methods to some extent (Table 1).

3.1.2 The NCA's Own Communications

In 21 countries (81%), the NCA indicated having their own bulletin or newsletter for communicating safety issues, either on a single issue or on multiple issues at a time (Table 1). Of these NCAs, nine always used this tool and 12 used it only occasionally. Fifteen countries (60%) published these bulletins on their website. Fourteen NCAs

distributed bulletins via email (54%) and four countries distributed them via an email sent by professional bodies (i.e. ES, FR, IE, NL). Distribution via post was only used by BG, CZ, LV, and SE.

In most countries, EMA press releases were also published on the NCA's website (24 of the 26; 92%). In 11 of these countries, this was done only when the safety issue was considered particularly relevant in the national context. In most countries, NCAs also indicated issuing their own press releases (21 of the 25; 84%) and involving main interest groups (21 of the 26; 81%) to increase awareness of a safety issue (Table 1). These main interest groups could comprise patient organisations, professional bodies, drug advisory committees, national health services and pharmaceutical companies who could all distribute safety news further to their members/contacts. The NCAs of two countries (RO and the UK) indicated they always directly contact main interest groups, whereas the other 19 NCAs did so on a case-by-case basis.

NCAs used various strategies to increase awareness among HCPs of new safety information on their website. Most NCAs used email alerts to which interested parties could subscribe (19 of the 25; 76%). Other strategies that were accessible in many countries were urgent safety message cascade systems where messages were sent to the senior managers in the national health system and

forwarded on to the relevant HCPs as a priority (14 of the 25; 56%), RSS feeds (13 of the 25; 52%) and social media (12 of the 25; 48%). Of the strategies asked (see electronic supplementary material 1), the UK used the most number of different strategies (seven) followed by IT (six) and ES, FR, LV and NO (five).

3.1.3 Educational Materials

Ten NCAs published educational materials on their national website (40%) (Table 1). In the UK only, the NCA provided a link on its website referring to an external webpage where HCPs could find these materials.

3.2 Awareness and Preferences Regarding Safety Communication

Overall, 1766 GPs completed the survey about awareness and preferences regarding safety communication. The number of responders ranged from 25 GPs in DK to 847 GPs in ES (Table 2). Over half of the responders had an accreditation of more than 20 years (overall: 60%; mean of country percentages: 54%) and most were primarily employed in a community-based setting (overall: 96%; mean of country percentages: 96%). The majority of GPs always used an electronic prescribing system (overall: 82%; mean of country percentages: 87%).

3.2.1 Awareness of Direct Healthcare Professional Communications (DHPCs), NCA Communications and Educational Materials

Overall, awareness of DHPCs was high and GPs were more aware of DHPCs (overall: 94%; mean of country percentages: 91%) than of NCA national communications (overall: 89%; mean of country percentages: 79%) (Table 3). In ES, NO and SE, GPs were more aware of NCA communications than of DHPCs. Responders from NL were least aware of NCA communications (21%), followed, at a distance, by responders from HR (66%). Awareness of educational materials was 64% overall, ranging from 56% in DK to 76% in IE. In particular, awareness was low in the UK, DK and ES.

3.2.2 Preferences Towards Senders, Format, Repetition and Communication Channels

For all GPs, the highest valued senders of safety information were the NCA and professional bodies (Fig. 1a), whereas the least valued senders were lay press and pharmaceutical companies. Among the different countries, differences in GPs' preferences towards the senders were small. The pharmaceutical companies were valued

somewhat higher by GPs in HR and IT than by GPs in DK, NL, NO, SE and the UK. GPs in ES and IT evaluated EMA somewhat more positively than GPs in NL, NO, SE and the UK (Fig. 1b).

The preference for an electronic format (overall: 63%; mean of country percentages: 56%; range 36% in SE to 72% in ES) rather than a hardcopy format (overall: 22%; mean of country percentages: 29%; range 13% in ES to 47% in SE) varied per country (Table 3). GPs in DK, ES, IT, NO and UK had a preference for an electronic format, similar numbers preferred hardcopy formats than electronic formats in HR, IE and NL, while more GPs in SE preferred a hardcopy format over an electronic format.

Repetition of a safety message was seen as useful by 89% of responders, a percentage that was relatively similar among countries (range 80% in the UK to 97% in IT) (Table 3). The most preferred channels of communication were medicines reference books and national clinical guidelines (Fig. 2a); these channels are often available in hardcopy as well as electronic format. Differences in preferences among countries were small (Fig. 2b). GPs were also asked questions on alternative communication channels, which are currently not commonly used by NCAs. Point-of-care alerts and email were the most preferred alternative communication channels to stay up to date on drug safety issues (Fig. 3a). In particular, Spanish GPs appreciated email messages (Fig. 3b). Mobile (health) apps, mobile phone text messages and social media were much less preferred, especially by GPs from IE, NL, NO, SE and the UK. GPs in DK valued almost all channels quite negatively, except for personalised letters and medicines reference books.

4 Discussion

We provide an overview of current NCA safety communication practices in 26 European countries, and the awareness and preferences regarding these practices among 1766 GPs from nine of these countries. In general, the current safety communication practices seemed to be broadly similar among European NCAs. Awareness among GPs was very high for DHPCs and less for other communication strategies (the NCA's own communications and educational materials). NCAs and professional bodies were the most preferred senders of safety information, and medicines reference books and national clinical guidelines were the most important channels, with point-of-care alerts and emails being the most appreciated 'alternative' information channels. Repetition of a safety message was seen as useful by most of the responders, whereas preferences towards the format (electronic versus hardcopy) differed among countries.

Table 2 Demographic characteristics of general practitioners who completed the preference survey

	Total	Mean of country percentages	DK	ES	HR	IE	IT	NL	NO	SE	UK
Number included	1766		25 (1)	847 (48)	85 (5)	144 (8)	183 (10)	72 (4)	105 (6)	108 (6)	197 (11)
Female	959 (54)	51	15 (60)	530 (63) ^a	71 (84)	80 (56)	47 (26)	22 (31)	42 (40)	60 (56)	92 (47)
Age, years											
<35	158 (9)	9	–	85 (10)	24 (28)	15 (10)	2 (1)	4 (6)	6 (6)	12 (11)	10 (5)
35–45	432 (24)	28	14 (56)	207 (24)	22 (26)	45 (31)	4 (2)	21 (29)	28 (27)	29 (27)	62 (31)
46–55	606 (34)	29	4 (16)	338 (40)	31 (36)	39 (27)	41 (22)	22 (31)	29 (28)	21 (19)	81 (41)
>55	570 (32)	34	7 (28)	217 (26)	8 (9)	45 (31)	136 (74)	25 (35)	42 (40)	46 (43)	44 (22)
Primary employment setting											
Community-based	1551 (96)	96	25 (100)	809 (96)	84 (99)	125 (87) ^{ab}	163 (89)	72 (100)	102 (97)	104 (96)	192 (97)
Hospital-based	39 (2)	1	–	30 (4)	–	1 (1) ^{ab}	2 (1)	–	2 (2)	3 (3)	2 (1)
Other	32 (2)	3	–	8 (1)	1 (1)	19 (13) ^{ab}	18 (10)	–	1 (1)	1 (1)	3 (2)
Accreditation, years											
<5	128 (7)	9	4 (16)	66 (8)	22 (26)	7 (5)	2 (1)	3 (4)	6 (6)	12 (11)	6 (3)
5–20	579 (33)	37	12 (48)	271 (32)	36 (42)	58 (40)	19 (10)	36 (50)	42 (40)	40 (37)	65 (33)
>20	1059 (60)	54	9 (36)	510 (60)	27 (32)	79 (55)	162 (89)	33 (46)	57 (54)	56 (52)	126 (64)
Electronic prescribing system											
Yes, always	1446 (82)	87	24 (96)	661 (78)	74 (87)	118 (82)	167 (91)	69 (96)	99 (94)	103 (95)	131 (67)
Yes, but not always	290 (16)	11	1 (4)	173 (20)	10 (12)	22 (15)	12 (7)	3 (4)	3 (3)	5 (5)	61 (31)
No	30 (2)	2	–	13 (2)	1 (1)	4 (3)	4 (2)	–	3 (3)	–	5 (3)

Data are expressed as *n* (%)

DK Denmark, ES Spain, HR Croatia, IE Ireland, IT Italy, NL The Netherlands, NO Norway, SE Sweden, UK United Kingdom

^a One responder did not complete this question^b Responders could give multiple answers

Table 3 General practitioners' awareness of DHPCs, NCA communications, and EMs, and preferences on format and repetition

	Total	Mean of country percentages	DK	ES	HR	IE	IT	NL	NO	SE	UK
Awareness											
Aware of DHPCs	1652 (94)	91	24 (96)	816 (96)	81 (95)	138 (96)	165 (90)	62 (86)	89 (85)	88 (81)	189 (96)
Aware of NCA com.	1571 (89)	79	20 (80)	820 (97)	56 (66)	136 (94)	151 (83)	15 (21)	100 (95)	93 (86)	180 (91)
Aware of EM	995 (64)	65	14 (56)	533 (63)	56 (66)	110 (76)	121 (66)	49 (68)	^a	^a	112 (57)
Format preference ^b											
Hardcopy	389 (22)	29	5 (20)	112 (13)	23 (27)	63 (44)	48 (26)	28 (39)	23 (22)	50 (47)	37 (19)
Electronically	1116 (63)	56	15 (60)	610 (72)	41 (48)	66 (46)	113 (62)	33 (46)	69 (66)	38 (36)	131 (67)
No preference	258 (15)	16	5 (20)	123 (15)	21 (25)	15 (10)	22 (12)	11 (15)	13 (12)	19 (18)	29 (15)
Repetition seen as useful ^c	1565 (89)	87	21 (84)	768 (91)	80 (94)	129 (90)	177 (97)	58 (81)	86 (82)	89 (82)	157 (80)

Data are expressed as *n* (%)

DK Denmark, ES Spain, HR Croatia, IE Ireland, IT Italy, NL The Netherlands, NO Norway, SE Sweden, UK United Kingdom, DHPCs direct healthcare professional communications, NCA com. national competent authority communications, EM educational materials

^a Question not included in the survey for NO and SE

^b Three responders did not complete this question (two responders from ES, one from SE)

^c Three responders did not complete this question (two responders from ES, one from IE)

Below, we discuss some recommendations and guidance for future safety communication practices, specifically based on the results of the nine countries included in both the assessment of current safety communication practices and the GPs' awareness and preferences survey.

4.1 DHPCs

In our study, 92% of GPs were aware of DHPCs, which implies that the 'cornerstone' of NCA (and pharmaceutical company) safety communication at least reaches this important target population. Awareness may have increased over time as, in our study, 86% of GPs from NL reported being aware, compared with 72% in a previous study [3]. Possibly, as the number of DHPCs issued has steadily increased in the past 15 years [7], GPs are more likely to have received a DHPC that concerned a medicine they encounter in their clinical practice. However, other factors, such as differences among the included GPs, cannot be ruled out as factors affecting the high reported overall awareness.

Most NCAs publish DHPCs on their website. Additional dissemination via electronic means or patient organisations and/or professional bodies is used to a much lower extent. Such alternative dissemination strategies could be used to further increase awareness of DHPCs. Nevertheless, awareness was not higher in each of the countries using additional dissemination strategies. For instance, NCAs in NL and NO additionally disseminate via electronic means,

but GPs' awareness of DHPCs was lower than in most of the other countries, possibly because only a few GPs had subscribed to this voluntary service.

GPs' awareness of DHPCs was highest in most countries that also used patient organisations and/or professional bodies to disseminate safety messages, which suggests that this can be a helpful strategy to increase awareness (Table 4, recommendation a). However, a causal association cannot be made and the pattern does not apply for all countries (i.e. awareness was relatively low in NL, in which this dissemination tool was also used). ES was the only country in which the NCA allows pharmaceutical companies to distribute DHPCs by email through professional bodies without also sending a hardcopy version. Interestingly, GPs' awareness of DHPCs was very high in ES, and was higher than in several other countries (i.e. NL, IT, NO, SE, HR). This may be associated with the finding that professional bodies are the preferred senders of safety information, and suggesting that providing only an electronic version of a DHPC does not negatively influence GPs' awareness of DHPCs. Sending DHPCs through professional bodies, who are considered reliable senders of safety information, may also result in better adoption of the message and have a larger impact on prescriber behaviour.

4.2 NCA Communications

A bulletin or newsletter with an update on multiple or single safety issues was available in 81% of the European

Fig. 1 a Preferences towards various senders of safety communication: “How do you value the following sources as a sender of safety messages [on a Likert-scale from 1 (very negative) to 5 (very positive)]?”. **b** Preferences towards various senders of safety communications per country: “How do you value the following sources as a sender of safety messages [on a Likert-scale from 1 (very negative) to 5 (very positive)]?” Means per country with 99% confidence intervals. *Solid, horizontal, red line* indicates mean of the total sample; *dashed, horizontal, red line* indicates mean of the country means. *DK* Denmark, *ES* Spain, *HR* Croatia, *IE* Ireland, *IT* Italy, *NL* The Netherlands, *NO* Norway, *SE* Sweden, *UK* United Kingdom, *NCA* national competent authority, *EMA* European Medicines Agency

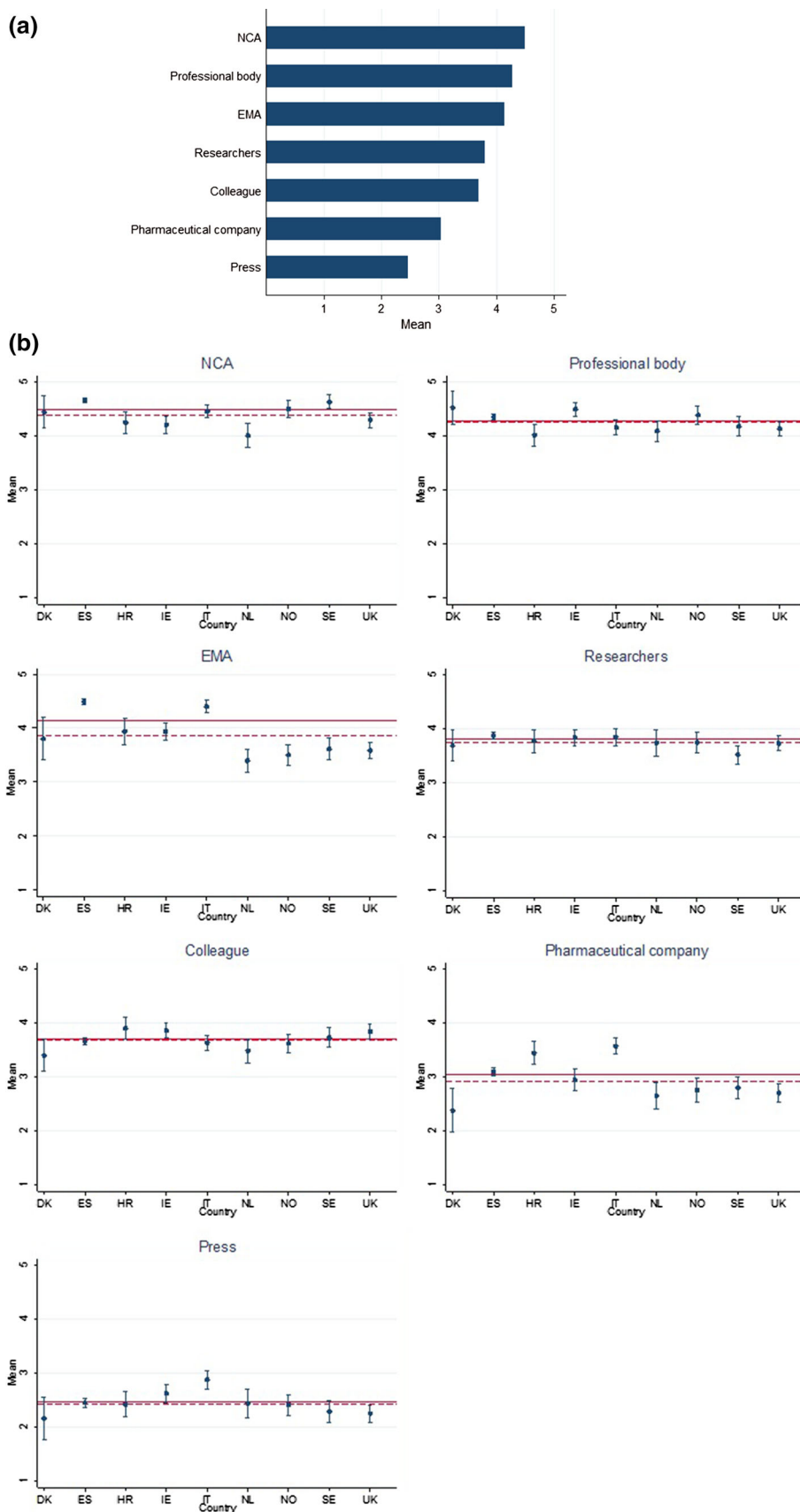
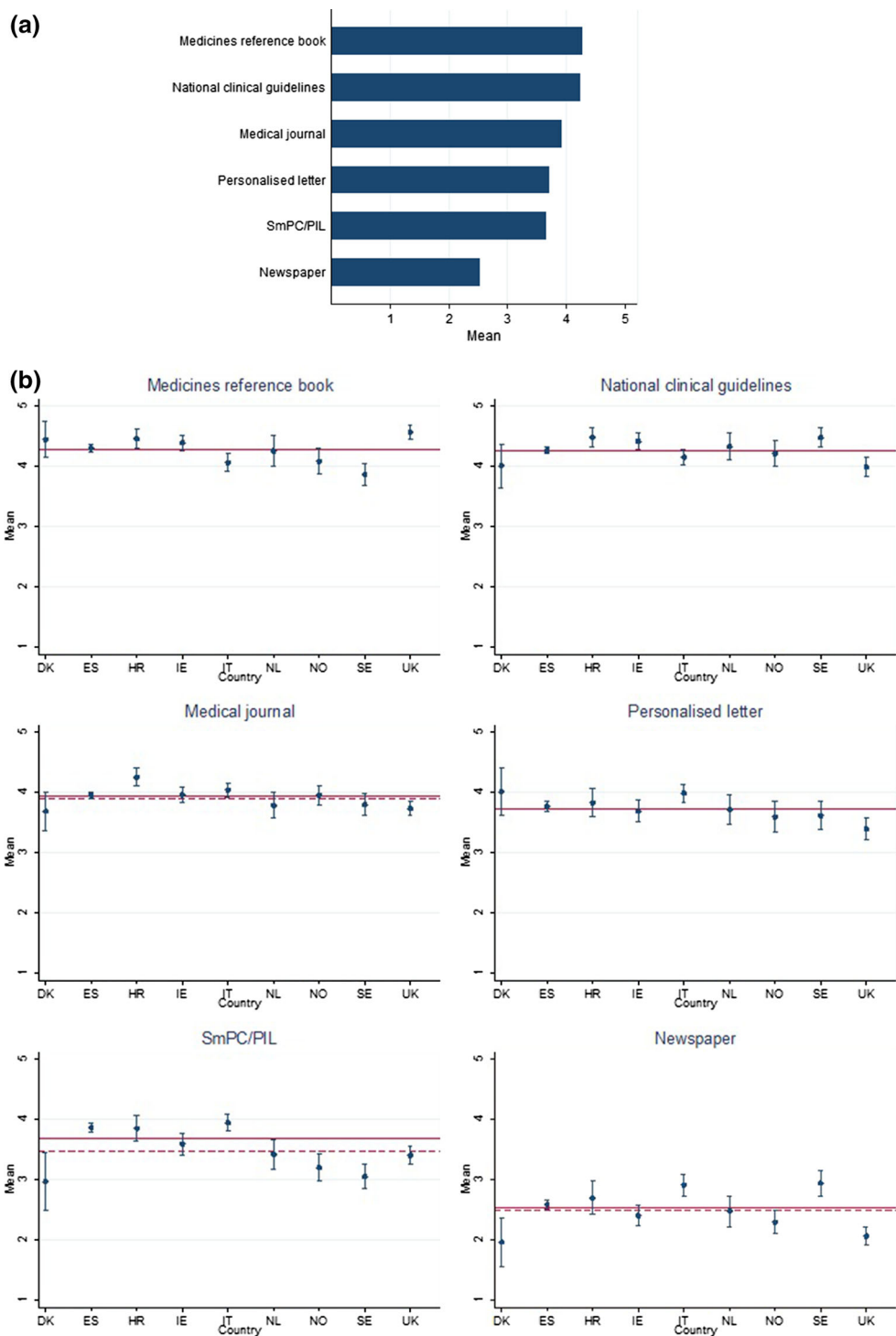


Fig. 2 a Preferences towards various channels of safety communications: “How do you value each channel to keep up to date on the safety of medicines [on a Likert-scale from 1 (very negative) to 5 (very positive)]?”. **b** Preferences towards various channels of safety communications per country: “How do you value each channel to keep up to date on the safety of medicines [on a Likert-scale from 1 (very negative) to 5 (very positive)]?”. Means per country with 99% confidence intervals. Scale 1 (very negative) to 5 (very positive). *Solid, horizontal, red line* indicates mean of the total sample; *dashed, horizontal, red line* indicates mean of the country means. *DK* Denmark, *ES* Spain, *HR* Croatia, *IE* Ireland, *IT* Italy, *NL* The Netherlands, *NO* Norway, *SE* Sweden, *UK* United Kingdom, *SmPC* summary of product characteristics, *PIL* patient information leaflet



countries included in this study. In other countries, the NCA may also consider issuing a bulletin or newsletter since the NCA was seen as a preferred sender of safety information (Table 4, recommendation b). Nine countries always issued the bulletin or newsletter, while 13 did so only occasionally. In ES, the awareness of NCA communications was highest, which may reflect the proactive

communication, using professional bodies and regional bodies for amplifying safety messages. The survey indicated that countries use, to various degrees, different electronic communication strategies (e.g. RSS feeds, email alerts). These strategies require relatively modest investments, and, although their uptake by HCPs is not yet large, this could be expected to increase with time. However, in a

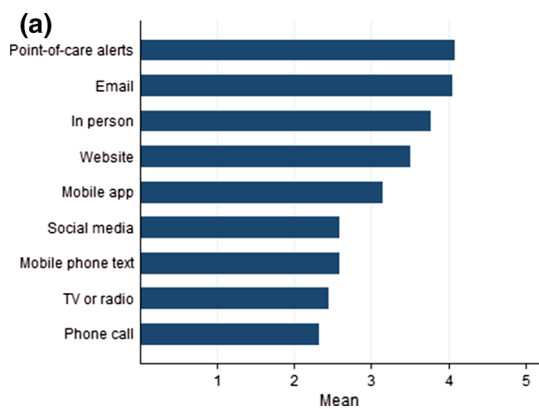


Fig. 3 a Preferences towards various alternative channels of safety communications: “How do you value the following alternative channels to keep up to date on the safety of medicines [on a Likert-scale from 1 (very negative) to 5 (very positive)]?”. **b** Preferences towards various alternative channels of safety communications per country: “How do you value the following alternative channels to keep up to date on the safety of medicines [on a Likert-scale from 1 (very negative) to 5 (very positive)]?” Means per country with 99% confidence intervals. Scale 1 (very negative) to 5 (very positive). *Solid, horizontal, red line* indicates mean of the total population; *dashed, horizontal, red line* indicates mean of the country means. *DK* Denmark, *ES* Spain, *HR* Croatia, *IE* Ireland, *IT* Italy, *NL* The Netherlands, *NO* Norway, *SE* Sweden, *UK* United Kingdom, *app* application

fast-changing digital work environment, a specific tool may be quickly outdated or superseded by a newer tool.

4.3 Educational Materials

Of the specific safety communication tools assessed in this survey, GPs were least aware of educational materials. Educational materials, developed by pharmaceutical companies, may not have been available for long enough, or issued for a large enough number of products prescribed by GPs, to be recognised. One review showed that printed educational materials had a small positive effect on HCPs’ practices [8], whereas another review showed no impact on patient outcomes, HCPs’ knowledge and HCPs’ behaviour [9]. While the design of educational materials is shown to be important for their practical use [10], our survey suggests that awareness needs to be improved, but that a clear endorsement by NCAs (as a more trusted source than pharmaceutical companies) is probably needed to generate sufficient impact. In open-ended questions, some GPs warned that glossy materials were considered as advertising and were therefore less trustworthy (Table 4, recommendation c).

4.4 Format

In particular, Spanish GPs preferred electronic communication tools. The current safety communication practices in

ES may have influenced this finding since pharmaceutical companies are allowed to distribute DHPCs electronically through professional bodies and NCA communications are sent electronically. Furthermore, DHPCs, educational materials and NCA communications are published on the NCA’s website. However, the finding that Swedish GPs preferred a hardcopy format over an electronic format, despite the fact that the NCA in Sweden also publishes DHPCs and bulletins on its website, does not support this hypothesis. Another reason for the high preference for electronic communication tools in ES could be the relatively high number of responders aged ≤ 55 years; however, responders from HR were also relatively younger and their preference for an electronic format was much lower. Taken together, the reason for country differences is unclear and the differences suggest that one should consider country-specific format choices (Table 4, recommendation d).

4.5 Repetition

Most GPs considered repetition of safety information useful. A previous study showed that HCPs (i.e. GPs, internists, pharmacists) found repetition moderately useful [3]. There may be differences among professions in their preference for repeating safety information but this should be further assessed. For GPs, repetition seems to be useful, although it should not cause alert fatigue (Table 4, recommendation e).

4.6 Senders

Only a few countries used patient organizations and/or professional bodies in the distribution of both DHPCs and NCA communications. It is recommended other countries consider this strategy since professional bodies and NCAs were the most preferred senders of safety information (Table 4, recommendation a). NCAs should take this into consideration when distributing safety communications since current proactive distribution of DHPCs and educational materials relies heavily on pharmaceutical companies, which are considered less reliable by GPs.

4.7 Channels

Of the channels that are available in both hardcopy or electronic format, the medicines reference books and national clinical guidelines were the most preferred channels for keeping up to date on safety information. Collaboration with authors of these channels seems important to ensure regular updates of such information (Table 4, recommendation f).

Fig. 3 continued

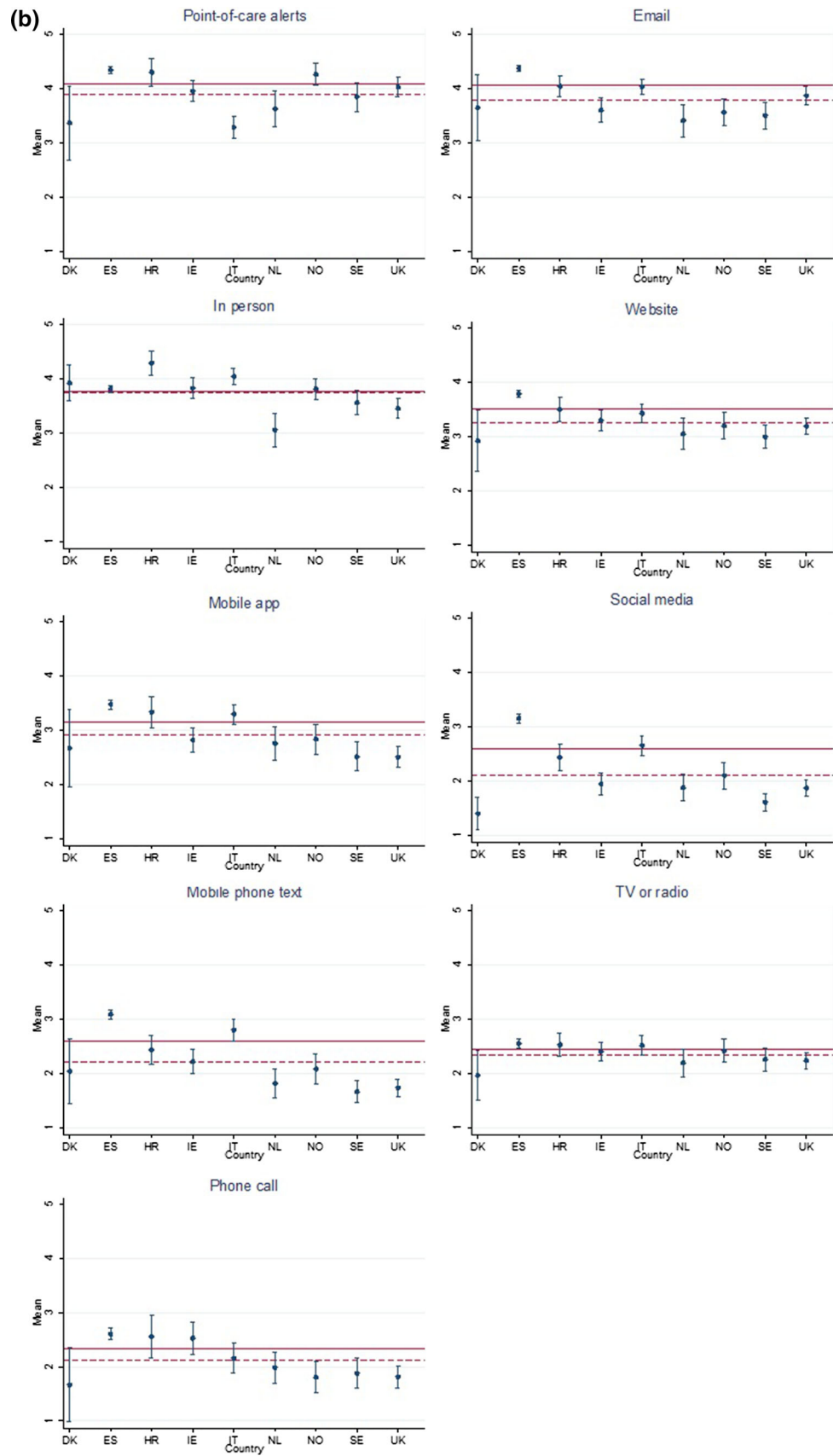


Table 4 Recommendations and guidance for future safety communication practices towards general practitioners

-
- (a) Use a preferred and clearly identifiable sender (i.e. NCA and/or professional body). Patient organisations/professional bodies could be used to (further) distribute safety communications where relevant
 - (b) NCAs should explore issuing a bulletin to repeat DHPC safety messages
 - (c) Increase awareness of educational materials and ensure that they are clearly distinguished from promotional material
 - (d) Format and channels of communication tools should be tailored to national preferences
 - (e) Repetition may be useful but one should be aware of 'alert fatigue'
 - (f) Collaborate with authors of medicines references books and national clinical guidelines regularly as these are positively evaluated channels of safety information
 - (g) Explore the use of point-of-care alerts
-

NCA national competent authority, *DHPC* direct healthcare professional communication

Several alternative channels can be used to provide immediate safety information. Of these, point-of-care alerts (Table 4, recommendation g) and email were the generally preferred methods, while mobile phone text and social media were not highly rated. Some country-specific preferences can be considered for successful safety communication (Table 4, recommendation d).

4.8 Strengths and Limitations

The strength of this study is the use of surveys collecting data from a wide range of European countries, which made it possible to compare current safety communication practices with GPs' preferences and to assess differences among countries.

A limitation of the study is that the assessment of NCA safety communication practices was conducted in 2014, whereas the survey data among GPs were collected in 2015. Some changes in communication practices in Europe may have occurred since 2014. Furthermore, responders may have interpreted specific communications differently. We therefore explicitly asked Work Package 6 active partners to check the provided answers. In total, 11 changes were made, of which eight related to NCA communications. Confusion about NCA communications was not unexpected since in some countries they contain an overview of distributed DHPCs. These NCA communications are still in various stages of development.

A limitation of the survey among GPs is the large variation in the number of GPs per country. Almost half of the included GPs were from ES and only a small number were from DK. Therefore, overall percentages were driven by the responders from ES. We also presented the mean of country percentages to control for this influence. The large variation may be due to differences in the total number of GPs in the different countries. The included number of GPs represented between 0.3% (for UK) and 3.7% (for IE) of the total number of GPs in the various countries (see electronic supplementary material 2). Variation across

countries was also shown in the characteristics of the GPs. For instance, the number of females was relatively high in HR, and the number of responders aged >55 years was relatively high in IT. Therefore, country differences may not only be caused by differences in current practices but also differences in the underlying population.

Such differences in sex and age distribution across countries are also shown in the total GP population of the different countries (see electronic supplementary material 2). This suggests that the sample of GPs included in our study may be representative of the total GP population in a specific country. However, it should be noted that there are some differences between the sample of GPs in our study and the total GP populations [for instance, the number of female GPs in IT was much lower in our sample than in the total Italian GP population (26 vs. 41%)]. In addition, representativeness of the responders with respect to other characteristics is not known. Another aspect related to representativeness is the way in which the survey was distributed among HCPs. For instance, HCPs contacted through email addresses available at the NCA may differ from HCPs for whom the NCA does not have their email address. Finally, social desirable answering may have occurred in this study, where GPs were asked to indicate, for instance, whether or not they were aware of different types of safety communications.

4.9 Future Studies

General communication theory defines several variables that are important for how information can be effectively transferred, i.e. the source, message, channel, receiver and target factors [11]. Our study revealed some knowledge about several aspects of this theory, i.e. the message (format and repetition), source (senders), channels and awareness (outcome variable). Future studies may focus on the characteristics of the receiver of information, such as personality traits, to target safety messages more individually. Moreover, future studies should also evaluate impact

in terms of process outcomes such as prescribing behavior or clinical outcomes (adverse events) [12].

Previous research about educational materials showed that some characteristics of the materials may have a larger potential to influence effectiveness (e.g. the source of information, format) than others (e.g. frequency) [8]. Future studies are needed to test which of these aspects are relevant for other types of safety communications.

Interestingly, in the countries with an equal number of GPs preferring both a hardcopy and electronic format (i.e. HR, IE and NL), the NCA used fewer different electronic communication strategies to increase awareness of safety issues on their website (three to four different strategies, compared with four to seven strategies used in other countries). Future studies may assess whether the use of additional efforts influence GPs' preferences as to the format in which safety communications are distributed.

5 Conclusion

NCA's use similar methods for safety communications on medicines. Repetition of a safety message was generally considered useful, and the NCA and professional bodies were preferred senders of safety information. In some countries, awareness of NCA communications and educational materials was low, indicating that specific efforts should be made to make GPs more aware of such communications. The preference for an electronic format and specific (electronic) channels was low in some countries, implying that further promotion and research may be needed before relying entirely on such media in these countries.

Acknowledgements The assistance of the HCPs from Sweden, Norway, Denmark, the UK, The Netherlands, Ireland, Spain, Italy and Croatia, as well as staff from NCA's who responded to the surveys, is greatly appreciated. Special thanks go to Jess Hearn for her contribution during the initial phases of the project.

Other SCOPE Work Package 6 members include F. Boudier, Y. Escudero, J. García, Y. Knudsen, L. Loughlin, M. A. Maciá, L. Michan, A. Rodriguez, H. Samdal.

Author contributions All authors contributed to the development and formulation of the research question. AW and JAR collected the data on the survey relating to the NCA's methods of risk communication, and SCOPE work package 6 members from the UK collected the data of the survey about web-portals. For the survey relating to the awareness and preferences of GPs, STdV, MJMvdS and PGMM collected the data in The Netherlands, AC and IB collected the data in Italy, AMC collected the data in Ireland, DM collected the data in Spain, IS and AA collected the data in Croatia, AW and JAR collected the data in Sweden, and the other SCOPE Work Package 6 members collected the data in the remaining countries. For this study, STdV analysed the data of the three surveys, and all authors contributed to the interpretation of the results. STdV wrote the manuscript, and MJMvdS, AC, IB, AMC, DM, IS, AA, AW, JAR, PD and PGMM reviewed and edited it. All authors read and approved the final version of the manuscript.

Compliance with Ethical Standards

Ethical approval was not considered necessary due to the nature of this study (survey among regulatory agencies and HCPs). Participants were assured that all sensitive data would be kept confidential.

Funding This work was conducted in the context of a European Commission-sponsored joint action—Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE). Any opinions, conclusions and proposals in the text are those of the authors and do not necessarily represent the views of the European Commission or NCA's. The survey among European HCPs was made possible through a tendered subcontract ITT-1301, ECM-2294.

Conflict of interest Sieta T. de Vries, Amelia Cupelli, Ilaria Baldelli, Anna Marie Coleman, Dolores Montero, Ivana Šipičić, Adriana Andrić, Annika Wennberg, Jane Ahlqvist-Rastad and Petra Denig have no conflicts of interest to declare that are directly relevant to the content of this study. Maartje J. M. van der Sar and Peter G. M. Mol are employees of the Dutch Medicines Evaluation Board.

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