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Title: A cross-sectional study on substandard and falsified medicines (fake or counterfeit drugs) in UK pharmacies during the COVID-19 pandemic.

Abstract

Background

Failure of the Falsified Medicines Directive (FMD) in the UK could mean that substandard and falsified medicines (SFs) enter the legitimate supply chain. Does this risk UK patients' health? Readiness to implement FMD, prevalence of SFs vs. regulator detection were assessed.

Research design and methods

12,040 primary care pharmacies across England were invited (Apr 2021-Mar 2022). Respondent postcodes were used to extract deprivation scores. Information request was placed with the medicine's agency. Survey findings were used to calculate probability and power of a simulated fictitious trial.

Results

208 participants responded: Of the 7 who identified SFs, all but 1 reported it, 61% were ready to implement FMD, 74.1% had adequate resources, 54.8% considered FMD would improve patient safety, 17.8% had ever reported SFs. SFs were prevalent in deprives areas. Bayesian simulation shows 438 (p=0.030) incidences with a 3% probability of UK SFs prevalence. The agency identified 15,238 units in the legitimate supply chain in 2019 and 2020. Results are credibility, reliability and generalizable, with corroborated longitudinal persistence.

Conclusions

FMD or equivalent processes need to be urgently reinstated. Deprived children maybe more affected. Pharmacists are worried about liability. All health consultations should assess safety, and effectiveness of medicines. Findings should inform policy, systems planning, surveillance and evaluations.

Keywords:

Counterfeit Drugs; Curriculum; Delivery of Health Care; Developed Countries; Liability, Legal; Patient Care; Pharmaceutical Services, Online; Pharmacies; Pharmacovigilance; Prescriptions; Public Health.

Abbreviations

Analysis of variance (ANOVA)
Department of Health (DoH)
Deprivation Affecting Older People Index (IDAOPI)
European Medicines Agency (EMA)
European Union (EU)
Falsified Medicines Directive (FMD)
Freedom of Information (FOI)
General Pharmaceutical Council (GPhC)
Index of Multiple Deprivation (IMD) 2019
Income Deprivation Affecting Children Index (IDACI)
Index of Multiple Deprivation (IMD) 2019
Local Pharmaceutical Committees (LPCs)
Medicines Healthcare Products Regulatory Agency (MHRA)
Observational Studies in Epidemiology cross-sectional reporting guidelines/ Standards for QUality Improvement Reporting Excellence (SQUIRE)
Pharmaceutical Services Negotiating Committee (PSNC)
Royal Pharmaceutical Society (RPS)
Substandard and falsified medicines (SFs)
The General Pharmaceutical Council (GPHC)
The United Kingdom (UK)
World Health Organisations (WHO)
Yellow Card Reports (YCR)

1. Introduction

Falsified Medicines Directive (FMD 2011/62/EC)[1] has been incorporated into UK domestic legislation and requires vigilance against substandard and falsified medicines (SFs). For this paper, World Health Organisations (WHO)'s definitions of SFs are used: Substandard medicines are those not up to pharmacopeial standards e.g., become degraded after manufacturing due to poor storage contribute towards phenomena such as antimicrobial resistance. Falsified medicines are those medicines that intentionally misrepresent themselves, i.e., fake/counterfeit medicines. Through Brexit, the UK lost access to the European central database which, in practice has resulted in a lack of drug because verification equivalent national dataset has not been created by the medicines regulator like those in Europe. However, all major companies can and are willing to provide the UK government a list of batch numbers and expiry dates of legitimate drugs that would be reasonably easy to set up a domestic database across the UK to be able to deliver on this work. This further bolsters and links with the WHOs requirement to protect the general public against SFs.

The UK is compliant with the WHO's basic standard of having a system in place for detecting and reporting fake drugs i.e., the Yellow Card Reports (YCR) system[2], which are known to be underutilized[3–6]. The YCR is a spontaneous reporting pharmacovigilance system, which invites reports of suspected side effects to medicines, vaccines, e-cigarettes, medical device incidents, defective or falsified (fake) products to the Medicines and Healthcare products Regulatory Agency (MHRA) to ensure safe and effective use. YCR the sole means of safeguarding against SFs, which research suggests is not fully representative of practise including what risks are appearing at frontline and what pharmacists are doing to safeguard patients' lives.

Most pharmacies should have been ready for FMD implementation in February 2019, but were not[7]. However, Brexit (exit date 31st Dec 2020) resulted in the suspension of access to the central database held at the European Medicines Agency (EMA) within Europe. The spread COVID 19 pandemic further reduced governmental priority to renegotiate access to this database or to set up an equivalent domestic one. This meant that practically this directive was undeliverable as an equivalent UK database has not been set up, making it impossible to comply with. However, the legislative framework still requires the UK to comply in line with the World Health organisation's guidance to minimise harm from SFs. As a result of this confused position, readiness needs to be reassessed to look for progress or regress of the earlier position.

Prior work[7] demonstrates a lack of compliance with the FMD directive, which means that SFs can enter the UK market through legitimate supply chains. Pharmacists protect public health, but this is not apparent in research data. With the growing commercial pressure to decouple onsite supervision by pharmacists in pharmacy may also mean that the move towards remote supervision happens without proper risk-analysis, potentially widening a governance gap. Collectively, does this mean UK patients are more at risk of fake and falsified medicines (Research Question)?

2. Methods

This survey has been previously validated[7,8] and the survey instrument is available to use freely. An electronic survey invited 12,040 email address of registered pharmacies across England by unique contractor code, thus inviting responsible pharmacists working in these premises (Start 26 Apr 2021, End 31 Mar 2022) with follow-up of non-responders. All participants gave written informed consent. A sample size calculation (95% confidence level, 12040 population size, with a 7% margin of error) resulting in a minimum ideal sample size of 193 responses to be representative. Respondents were

invited to provide self-reported answers. Missing data and subgroup analysis is presented and described. Comments are thematically analysed.

While it would not be ethically feasible to conduct a trial on this concept, simulation methods were used to calculate a fictitious trial with the discovered probability of detecting SFs to find its power. Bayesian methods can provide a more refined representation of the true probabilities. Assuming each of these trials as independent Bernoulli trials/coin toss (e.g. Detected SFs or not Detected SFs), the outcome of a simulated fictitious trial using the TrialSize package[9] (5% significance level, pharmacy population 12,040), estimated trial power was 100%, indicating highly reliable study findings. See 'Supplementary file 1 Syntax' for full simulation syntax.

Anonymous responses were collected along with post-code. Live postcodes were validated, and deprivation scores extracted. Postcodes of pharmacies were linked with freely available data on Indices of Multiple Deprivation (IMD) 2019[10] as earlier work suggest there is a link between detection of SFs with areas of higher deprivation (i.e. poorer areas). Postcodes were mapped using ArcGIS online and can be freely viewed https://arcg.is/1aby44 . A Freedom of Information (FOI) request was also placed with the medicine's competent agency. FOI requests can be made by any member of the public to a government body. If the information is in the public interest, the government body is normally obliged to release that information within 20 working days. If it is unreasonable to extract the information from their systems or is not in the public interest, this information can be withheld. This is a general principle adopted by many OECD nations.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Reporting is in line with the Strengthening the Reporting of Observational Studies in Epidemiology cross-sectional reporting guidelines/ Standards for QUality Improvement Reporting Excellence (SQUIRE) guidelines.[11] Favourable institutional ethical approval was obtained and this study followed the declaration of Helsinki principles. Authors confirm that they obtained consent from all participants. No financial (or similar) benefits were offered to minimise biased responses.

3. Results

Results are presented below in separate segments: section 3.1 independent Freedom of Information (FOI) requests, section 3.2 quantitative survey analysis, section 3.3 qualitative survey analysis, section 3.4 deprivation (3.4.1 Mapping) and section 3.5 Simulation.

3.1 Freedom of Information

FOI request with the MHRA suggested that there were 15,238 units of falsified medicines in the UK legitimate supply chain in 2019 and 2020 (FOI reference numbers: '20 326', '20 416' and the same quoted response to the author). Repeated requests by the author about the definition of the word *"unit"* have not been answered. This raises doubt about the details of information collected or the opacity with which the agency has responded. However, it is clear that at least 15,238 solid doses (or equivalent) have been detected within the legitimate supply chain, but theoretically this could also relate to original packs (e.g., 28-84 tablets/capsules), outer packs /box-load or even pallet loads.

3.2 Quantitative

Response from 208 participants (208/12040 or 1.73% response rate) was achieved. Participant characteristics are described in table 1. The results meet the sample size calculation presented in the methods section, suggesting a sufficient response rate making the study findings generalizable.

Table 1 participant characteristics

	Frequency	Percent	P-value
Gender			**Chi-Square <0.001; overwhelmingly male**
Male	131	63.0	
Female	64	30.8	
Prefer not to say	7	3.4	
Prefer to self-describe	1	0.5	
How many years have you been a registered pharmacist?			**Chi-Square <0.001**
Unanswered	4	1.9	
0-5	35	16.8	
6-10	28	13.5	
11-15	33	15.9	
16-20	17	8.2	
20+	91	43.8	**Overwhelmingly well-experienced**
What type of pharmacy do you work in?			**Binomial 0.181 Retain the null. i.e., even distribution between independent and chain pharmacies**
Unanswered	6	2.9	
Independent	111	53.4	
Chain	91	43.8	
What are your current working hours per week as a pharmacist (excluding lunch)?			**Chi-Square <0.001**
Unanswered	4	1.9	
16 – 24	3	1.4	
25 - 34	20	9.6	
35 - 44	102	49.0	Full-time workers
45 - 54	62	29.8	
55+	17	8.2	
Have you or your patients ever identified substandard and falsified (SF) medicines? (Q7)			**Binomial <0.001. overwhelmingly not encountering SFs**
Yes	7	3.4	
No	201	96.6	
If so, did you inform the Medicines Healthcare Products Regulatory Agency (MHRA)? (Q7A)			**Binomial <0.001**
Unanswered	154	74.0	

Yes	12	5.8	
No	42	20.2	

Of the 7 people who identified SFs, all but 1 reported it to the MHRA. Those 7 individuals also: Contacted manufacturer, looked at tablets that were ordered via the internet by a patient, replaced patient stock while retained potentially SF stock for evidence, Informed the LPC/PCT at the time, informed the MHRA and contacted the Manufacturer, used a YCR to submit to the MHRA for ("Nystan® liquid set solid & wouldn't mix; substandard"). No harm came to the patient in these instances, other than potentially a missed dose. Three out of seven individuals had served patients who had purchased medicine online during the course of the pandemic, after which they sought help from their local pharmacy, indicating a level of trust in the profession.

Those who had not identified a SF medicine, went on to variously say what they would do in a similar circumstance which represented a combination of quarantining the product, informing colleagues referring patients appropriately for medical attention and reporting the information to a variety of stakeholders including the GPHC, the LPC, the PSNC, head office, wholesalers and related suppliers.

One individual mentioned *"I have encountered falsified medicines, but they were not supplied by my pharmacy. The police (rather than a patient) brought a bin bag full of falsified Viagra® to my pharmacy to destroy. I have also reported some potentially falsified medicine to the MHRA, but it transpired the medicine was genuine, just the manufacturer had temporarily been using alternate packaging to avoid a supply issue."*

Eight respondents said 'yes' patients have purchased medicines online during the pandemic and then sought help from the pharmacist.

Of the people who did not detect falsified medicines, 5 individuals reported that they helped patients deal with pharmaceutical issues related to medicines purchased online, with illustrative comments:

1. *"Yes. In some cases they obtained their prescriptions from an online pharmacy. Without seeing their prescription, the only advice we have been able to offer is general advice about their medicine. Where patients have obtained other medicines, again if they are licenced we can give them general advice and make them aware that not all medicines obtained online are not genuine and may be falsified. I offer personal opinion that I would never buy medicines online because one can never be sure that one is getting a genuine medicine."*
2. *"We always advice patients not to buy medicines online as there are many online websites selling substandard or SF. I personally have not across anyone of my service users who have reported such incidence."*

Study findings show that 81 (38.9%) respondents were 'Very much' and 46 (22.1%) were 'Somewhat' ready to implement FMD i.e., 61% were ready, which is a substantial improvement for the 6.8% recorded in August 2019[7]. While 32 (15.4%) said 'Not at all', 25 (12%) said 'Not really', 22(10.6%) were undecided, and 2 (1%) were unanswered.

On the question regarding adequate resources and equipment (e.g., computer terminals, scanners, compliance software, include initial set-up, IT, both software and hardware, plus ongoing operational costs) necessary to implement the FMD, findings show: 110 (52.9%) were 'Very much' ready, 44 (21.2%) 'Somewhat' ready, 1 (0.5%) unanswered, 18 (8.7%) saying 'Not at all', 23 (11.1%) saying 'Not really', 12

(5.8%) were undecided. This represents a 74.1% being ready with adequate resources as compared to 41.2% in August 2019[7], which is encouraging to see that progress is nevertheless being made by front-line pharmacies in being able to deliver on FMD.
On the question of these preparations, impacting business profitability, findings suggest 67 (32.2%) considered it 'Not at all profitable', 48 (23.1%) 'Not really profitable', 69 (33.2%) were undecided, 14 (6.7%) said 'Somewhat profitable', 8 (3.8%) 'Very much profitable' and 2(1%) were unanswered, indicating overall that operationally implementing FMD as being unprofitable.

On improving patient safety, findings suggest: 64 (30.8%) 'Very much improves patient safety', 50 (24%) 'Somewhat improves patient safety', 29 (13.9%) 'Does not improve patient safety at all', 25 (12%) 'Does not improve patient safety', 39 (18.8%) Undecided and 1 (0.5%) Unanswered. This data indicates 54.8% of respondents considered these preparations would improve patient safety, which is a reduction on earlier findings[7] of 77.5% on the same question, but in a smaller sample (n=102). Later thematic comments provide insight.

The percentage of medicines believed to be falsified in the UK were: <1% i.e., less than 1% 112 (53.8%), between 1 - 5% 65 (31.3%), between 6 - 10% 17 (8.2%), between 11 - 20%8 (3.8%), >21% i.e., more than 21% 3 (1.4%), with 3 (1.4%) unanswered.

In respondents' opinion, the percentage of medicines are believed to be falsified from online suppliers were less than half: between 0 – 20% 82 (39.4%), between 21 – 40% 62 (29.8%), between 41 – 60%40 (19.2%), between 61 – 80% 15 (7.2%), between 81 – 100% 5 (2.4%) and 4 (1.9%) unanswered.

Respondents were asked to rank the most likely source of falsified medicines: 1. Parallel import system (EU Member State or a country within the EEA) 159 (76.4%); 2. Foreign registered Internet pharmacies 131 (63.0%); 3. Professional falsifier/illicit trade 116 (55.8%), 4. From UK registered Internet pharmacies 29 (13.9%) and 5. Other 9 (4.3%). Other comments were further described *"Indian manufacturers", "product made in countries outside UK and EU", "Other sites which are not regulated e.g., on the dark net", "eBay, Facebook, marketplace, wish, unregistered websites selling drugs"* and other cities within the UK were identified e.g. London. This is a large jump from earlier findings, where 56.2% said 'internet pharmacies'[7]. In the intervening four year, the pandemic might have accelerated this trend firstly due to 1. supply chain shortages and the need to source from alternative routes and 2. patients purchasing habits moved online.

Frequently falsified medicines in the UK were thought to be: 135 (64.9%) Erectile dysfunction, 44 (21.2%) Weight loss, 15 (7.2%) Other, 4 (1.9%) Anti-cholesterol, 5 (2.4%) Cancer, 5 (2.4%) Heart medicines. Other comments were further described as: "*all of the combinations above", "antibiotics", "opioids, any expensive medicine or a medicine which is difficult to obtain on a genuine prescription such as Xanax, sleep disorder drugs, controlled drugs, skin altering meds", "Anxiolytics", "supplements, Xanax, Benzodiazepine".* With others saying *"I have [not] come across any but media reading identify cancer meds which [are] bought over the internet".*

The presentation of medicines that make pharmacist suspicious would include: 60 (28.8%) Different packaging to original packaging, 59 (28.4%) Different source (e.g. different manufacturer or country of origin), 50 (24%) Different product composition (e.g. ingredients including excipients), 19 (9.1%) Different distribution route, 13 (6.3%) Different labelling and 7 (3.4%) Other. Other comments were further described as: *"mainly the availability to purchase ANY POM medicine without a prescription",*

"multiple patient complaints for same brand", "Substandard or off-size packaging would be most likely", "Look and feel of the product" or a combination of all above.
While 188 (90.4%) of respondents correctly identified the MHRA is the correct competent agency to report spurious medicines to, it is alarming that 20 or 8.6% identified other agencies: 188 (90.4%) Medicines Healthcare Products Regulatory Agency (MHRA), 6 (2.9%) European Medicines Agency (EMA), 6 (2.9%) General Pharmaceutical Council (GPhC), 3 (1.4%) Department of Health (DoH), 3 (1.4%) Other e.g., head office 2 (1%) and Royal Pharmaceutical Society (RPS).

Figure 1 summarises data on pharmacy self-efficacy in managing SF events and patients are reported that. Their confidence in ability as well represented in this validated scale and corroborate earlier findings.

[Insert Figure 1 here]
The 11 items reliability statistics scale (see Figure 1) of 201 respondents were used to calculate a 70% Cronbach's Alpha (0.696 unstandardized, 0.702 Standardized Items). The within people, between items (10 degrees freedom) ANOVA with Tukey's Test for Non-additivity has a F-statistic of 13.711 (P<0.001) indicating significant number of respondents 'agree' with the statements, in addition to the scale being reliable.

'Ever reporting' was investigated: Only 37 (17.8%) had ever used the YCR Scheme for SFs while 171 (82.2%) had not (Binomial P<0.001). Of these, six had detected SFs and appropriately reported them. The predominant reason for this was because they had never needed to use this reporting mechanism, however, other answers included a lack of awareness of this mechanism that they didn't know they could use this mechanism.

Most pharmacists were aware of any technologies in place 156 (75.0%), while 52 (25.0%) were not (Binomial P<0.001). Some suggested: "*FMD but that was scrapped with Brexit"* which implies that the technology is not considered important or currently relevant, other said *"FMD scanners"* identifying technologies in place to detect SFs, and another referred to the original outer-packaging *"I assume will be hologram on package; I may be wrong"* and *"I understand a new database will be provided in time but we are not able to access the old EU one. Medicines Safety has suffered as a result of Brexit."*
Similarly, exactly half the participants had received SFs training 104 (50.0%). One respondent suggested this was limited to *"how to use the FMD scanner".*

3.3 Qualitative

Finally, the question 'how can falsified medicines reaching the public be reduced?' invited 162 comments ('Supplementary file 2 Comment how can SFs reaching the public be reduced'), which were thematically analysed. Major themes of pharmacy's role, improved product-packaging, supply-chain responsibilities, and wider governance with sub-themes were identified as shown in Figure 2.

[Insert Figure 2 here]

3.3.1 Pharmacy's role

1.1 It was acknowledged that pharmacy has an important role in maintaining public health and providing first line primary care advice around the safe and appropriate use of medicines within community. However, there was an acknowledgement that increasingly, patients are using online pharmacy services that may or may not be legal/safe and appropriate sources of information, however respondents could

not be sure because they did not always have longitudinal relationships in providing care for individual patients or access to their health care records.

1.2 Pharmacy level vigilance and information sharing across the supply chain (Comment 151-155).

1.3 There was also a call for self-declaration by pharmacies (or companies that operate them) regarding sourcing only legitimate medicines (Comment 2).

1.4 Further education and training for pharmacist and Pharmacy staff (Comment 3).

1.5 However what pharmacy can do is limited (See Comment 128).

3.3.2 Product-packaging

2.1 The product's outer packaging itself presented challenges as to a pharmacist because in most instances they were familiar with the standard presentation and appearance of the medication. Many sought further features to the outer packaging to improve trust in the product original source (Comment 5)

2.2 However, in some instances the different appearance of the same product via parallel import meant that the product's presentation was different raising concern around its authenticity.

1.3.3 Supply-chain

3.1 Many pharmacies reported that manufacturers, wholesalers and the supply chain as a whole had to play a greater role towards maintaining secure supply chains (Comment 6).

3.2 Ongoing checks should be done across the supply chain, not just at pharmacy level (Comment 7).

3.3 A closed supply chain loop was considered, but price pressures impacts were recognised (Comment 8)

3.4 Some indicated that domestic manufacturing of medicines should see a resurgence (Comment 9).

3.5 Lower cost of medication sold from bricks and mortars pharmacy was an economical solution to undercut and make alternative supply chains less attractive (Comment 157) .

3.6 While no explicit mention was made about them taking legal liability, it was implied that pharmacists cannot be expected as the terminal link in the chain to be legally responsible for the harm that may potentially come to patients if SFs were inadvertently being delivered to pharmacies (Comment 11).

3.3.4 Wider governance/regulation/control

4.1 Re-engage in the FMD directive - A simple call to reinstate a UK equivalent database verification system (Comment 12).

4.2 Government had an important role in preventing the sale of supply of medicines from non-UK sources. Some identified that in the UK 'direct to consumer' sales and advertisement is not allowed according to legislation and The Association of the British Pharmaceutical Industry (ABPI) rules, which puts it at a disadvantage globally. To level the playing field, foreign online medicine should be prohibited or heavily taxed (Comment 13). A specific and repeated call to block foreign or Internet pharmacies was invited (Comment 14) some went further to acknowledge other sources too (Comment 15).

4.3 Government also has a role in fighting SFs by providing fit for purpose legislation and governance structures for agencies to work efficiently (Comment 16). Better import checks and controls was expected (Comment 17).

4.4 The parallel import system was identified has a potential SFs source (Comment 18).

4.5 There was a call for better public education around safe medicines use (Comment 19).

Similarly, a further question was asked 'In your opinion, what role can pharmacists play in combating falsified medicines?' which invited 150 comments (Supplementary file 3) and repeated many of the themes discussed above.

3.4 Deprivation

3.4.1 Mapping

Postcodes were validated against English IMD 2019 and deprivation scores extracted using the lookup tool[12], including extracting Income Deprivation Affecting Older People Index (IDAOPI), Income Deprivation Affecting Children Index (IDACI) measures the proportion of all children aged 0 to 15 living in income-deprived families. IMD 2019 tool, validated 195 live postcodes, with 12 unmatched or incomplete postcodes in the data, which were not analysed. However, 205 post codes could be used to extract population level scores including on purchasing power, household income, educational attainment and population structure, which were analysed.

Visual application is freely available from https://arcg.is/1aby44 . This data provides the social context within which these pharmacies operated and their IMD 2019 scores, serve as a proxy of the deprivation in that local area. These postcodes were enriched using a 20-minute walking distance from each pharmacy because, most people in the UK, live within a 20 minutes' walk from a pharmacy[13,14].Table 2-4 represents these findings. Of keynote are the higher rates of deprivation (not statistically significant) observed in those pharmacies who reported detecting SFs, including in aspects of purchasing power, household income, educational attainment and single-family structure. University level education can misrepresent single homes especially in cities due to the temporary nature of student residency.

In the visual application, responding postcodes appear as black dots, the enriched layer appears as green dots, and the IMD 2019 base layer is colour graded (deep blue representing high levels of deprivation and light-yellow representing wealth as per the AS Score bands of > 0.42, 0.306, < 0.2). Visual clustering appears around cities including London, Manchester, Liverpool, Exeter, Birmingham, and Sunderland.

Table 2 Descriptive statistics of respondent within 20 Minutes' Walk Time. Standard Deviation (STD), currency represented in Great British Pounds (GBP), quintiles are 1/5 segments of the population.

	All Respondents (n = 205)		**All those who detected SFs (n = 7)**	
Descriptive Statistics	**Mean**	**STD**	**Mean**	**STD**
2020 Purchasing Power				
2020PurchasingPowerPerCapita	**£18,041.43**	£5,131.44	**£14,570.71**	£3,201.28
2020PurchasingPowerIndex	**96**	27	**77**	17
2020PurchasingPowerTotal	**£370,904,644.40**	£460,734,194.40	**£209,621,948.70**	£114,787,708.90

Households Income by quintiles.				
2020HHs 1st Quintile (Below 19706GBP)	**1800**	1464	**1741**	907
2020HHs 2nd Quintile (19706 to 28816GBP)	**1703**	1309	**1775**	984
2020HHs3rdQuintile (28817 to 38750GBP)	**1631**	1255	**1344**	657
2020HHs4thQuintile (38751 to 55033GBP)	**1642**	1619	**1019**	648
2020HHs5thQuintile (55034GBP and above)	**1818**	3312	**665**	489
Education Qualifications of individuals above the age of 16 years.				
2020Pop16+ Edu No Qualifications	**3410**	2601	**3571**	1721
2020Pop16Edu Level 1 Qualifications	**1925**	1363	**1585**	697
2020Pop16Edu Level 2 Qualifications	**2115**	1419	**1665**	725
2020Pop16Edu Level 3 Qualifications	**2040**	2057	**1600**	1426
2020Pop16Edu Level 4 Qualifications Above	**4510**	5935	**2124**	1486
2020Pop16EduFullTimeStudents	**1918**	3230	**1380**	1779
Population Structure				
Total Population	**19674**	17659	**14933**	7685
Total Households	**8594**	7470	**6546**	3275
Male Population	**9945**	9207	**7590**	4209
Female Population	**9729**	8483	**7343**	3507
2020TotalPopulationAge 60+	**3673**	2341	**2911**	1131
2020TotalPopulationAge 0-14	**3526**	3268	**2834**	1451
2020 Average Household Size	**2**	0	**2**	0
2019 Unemployed Population	**462**	543	**358**	332
2020 Marital Status Single	**8743**	10458	**6372**	4507
2020 Marital Status Divorced	**1669**	1247	**1317**	639
2020 Marital Status Married	**8111**	6508	**6222**	2641

Table 3 Index of Multiple Deprivation Decile 2019 scores for (n=195) live postcodes; Deprivation Affecting Older People Index (IDAOPI), Income Deprivation Affecting Children Index (IDACI)

Decile	**Index of Multiple Deprivation**		**IDACI**		**IDAOPI**	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
1	28	13.5	31	14.9	23	11.1
2	29	13.9	15	7.2	27	13
3	21	10.1	22	10.6	20	9.6
4	22	10.6	28	13.5	30	14.4
5	25	12	22	10.6	16	7.7
6	18	8.7	27	13	22	10.6
7	18	8.7	13	6.3	23	11.1

8	14	6.7	16	7.7	15	7.2
9	13	6.3	10	4.8	9	4.3
10	7	3.4	11	5.3	10	4.8
Total	195	93.8	195	93.8	195	93.8

However, after crosstabulation (Table 5) SFs were more frequently detected in deprives areas (IMD19<5). Table 3 shows pharmacist continue to operate in areas of deprivation with higher IDACI & IDAOPI. It is already known that fewer general practitioner clinics are located in such areas, but with better pharmacy coverage.

Table 4 Crosstabulation of Deprivation Decile against weather SFs were detected.

	Index of Multiple Deprivation Decile										**Total**
Detected SF meds	1	2	3	4	5	6	7	8	9	10	
Yes	3	1	0	1	0	0	2	0	0	0	7
No	25	28	21	21	25	18	16	14	13	7	188
Total	28	29	21	22	25	18	18	14	13	7	195
	IDACI Decile										Total
	1	2	3	4	5	6	7	8	9	10	
Yes	3	0	0	1	1	0	1	1	0	0	7
No	28	15	22	27	21	27	12	15	10	11	188
Total	31	15	22	28	22	27	13	16	10	11	195
	IDAOPI Decile										Total
	1	2	3	4	5	6	7	8	9	10	
Yes	0	2	2	1	0	1	1	0	0	0	7
No	23	25	18	29	16	21	22	15	9	10	188
Total	23	27	20	30	16	22	23	15	9	10	195

3.5 Simulation

The probability of detecting SFs in this study was 7 out of 208 which is approximately 3.37% indicating that only about 3% of pharmacists would detect SFs. If this proportion was accurate, then in a population of 12,040 pharmacies, 405 pharmacies would detect SFs (as pharmacies can employ more than one pharmacist). It should also be acknowledged that 6 out of 7 reported SFs to the MHRA, which would equate to 347 YCRs out of 12,040 pharmacies, indicating that 58 valid detections that would go unreported. This has serious implications for clinical practice and impact on public health and safety.

RStudios, using the binomial distribution [Syntax: ppois(q = 1, lambda = 7/208, lower.tail = F) equates 0.0005537444] that is to say the probability a pharmacist will detect SFs is 0.055% at any time. The same fictitious trial detects a mean number of detect SFs is 356 (p=2.561428 x 10^{-32} across England) with an average probability of 0.02956811 or 2.96%. As a result, across England approximately 2.96% of

pharmacists will detect SFs. However, there are approximately 716 community pharmacies in Wales, 1250 community pharmacies in Scotland and 531 community pharmacies in Northern Ireland, making the UK community pharmacy population 14537. In a similar way 438 (p=0.03013001 across UK) incidences would be detected with a probability of 0.03013001 or 3% to be generalizable to the UK. However, the numbers calculated above do not come close to the 15,238 units actually reported by the MHRA, suggesting findings are very conservative.

4. Discussion

4.1. Presented data

This study asks questions about detecting SFs and professional practices to keep patients safe which, is a regulatory obligation of all community pharmacists and this survey sheds light on contemporary practice. It would be ethically unfeasible to conduct a trial to find the true proportion and so, simulation offers an alternative means of verifying this logic and get a more accurate statistical representation in larger samples. This study supplies a probability of detecting SFs at 7/208. The quality and credibility of the survey findings are relatively high because of the highly experienced respondents (with 20 + years of registered experience), working full-time, and fair representation between chain and independent pharmacies. Respondent opinions are probably the most qualified because of their knowledge of medicines and expertise in routinely handling medicines: In 2019, community providers dispensed £9.08 billion worth of prescription medicines in England and similarly 1.12 billion prescription items dispensed[15]. As a result, respondents have spent a significant amount of their professional career handling medicines and advising patients on the appropriate use of medicines, making their opinion highly valuable. Presented data are found to be generalizable across the UK and provide first-of-its-kind analysis linking detection of SFs with postcodes of pharmacies, their local area deprivation, income, employment and familial structures further strengthening evidence on the links with deprivation. Recent reports of pharmacy closures in deprived areas due to lower business profitability[16], could mean that the primary care interface here is shrinking, further exacerbating health challenges. However, the simulation analysis presents insight into the credibility and reliability of these results, which are generalizable.

From these results, there is a sustained and clear evidence for the need to reinstate FMD or equivalent processes. Increased awareness of YCR system is also needed. Standardisation of global product packaging is important in helping pharmacist detect SF and in identifying false positives through the parallel imports system. Online sales of medicines theoretically could be made more expensive through taxation, encouraging patients to use local bricks and mortar pharmacy businesses that provide face-to-face consultation and support for the safe and effective use of medicines in addition to in-person sales. Removal of value added tax (VAT) from local community-based pharmacies should be considered. Higher SFs may affect children with direct harm to children's own health or indirectly through health harms experienced by parents or carers.

Pharmacists are in the frontline to identify and report SFs. However, some pharmacists answered the survey that their pharmacies are not ready to implement the FMD and that they do not have the proper resources and equipment to implement the FMD. This is likely happening because the lifted regulatory requirement to implement FMD, which no longer applies. It also means that the variety of pharmacies owned by different chains or independent businesses have variable practices, especially after Brexit, further diverging from European practises. While the working conditions are similar across the country,

on this particular aspect of sufficient equipment and resources, there is great variability due to the financial challenges the sector is facing in the current economic climate, because there is no additional government reimbursement to cover these set-up costs or incentives from improved profits.

Strengths and limitations: There are several strengths of this work which include the good distribution of responses across England in areas of deprivation and affluence, the consistency of response (high reliability score) and the use of a validated survey scale, making this study findings reliable and generalizable across England. Limitations to this work include the low response rate.

4.2. Implications for clinical practice:

Currently, risk of medicines falsifications across UK is above 'zero' at least and could be a serious public-health threat at worst. Legally, there is a concern that pharmacists could be held responsible for direct or indirect care provided to SFs affected patients. This type of original observational data presented is not coded in routinely collected health data and is currently 'invisible', except for this study. Clinical trial data which is considered gold standard of evidence is not available for this kind of epidemiological study and would probably not be ethically viable. Similarly, true statistics on SFs are difficult inherently to confirm due to the underground nature of these markets.

SFs detection rate is consistent with prior findings but in larger samples indicating that this is a persistent phenomenon longitudinally over at least a 4 to 5-year period and is corroborated through data requests, which quantify SFs detected. The study implies that already vulnerable individuals with low levels of educational attainment, low income and in deprived areas may be further exposed to SFs risks, linking determinants of health to risk of SFs. Consequently, greater vigilance and routine questioning on the safe and effective use of medicines should be engaged with during health consultations. Some scope exists in civic education within schools and colleges regarding sourcing medicines exclusively from reliable pharmacies and raising public health awareness around risks from spurious sources, in addition to teaching this concept within healthcare curricula.

Links to prior works: Prior policy and publications considered SFs to be of negligible risk to public health in high income countries, with evidence restricted to low-income nations[17–26]. The current study corroborates increasingly USA[27] and European findings[28–30] of SFs prevalence and is supportive of the observed notion that increasing use of online pharmacies is being made, whether or not they are registered in the UK or Europe i.e. potentially legitimate or illegitimate. With the increasing use of digital sources, there is a lack of face-to-face consultation and risks around safe use of medicines escalate i.e., either not be communicated properly or not acted upon urgently. Additional arguments around health professional liability in instances where patients litigate - where local community practitioners are more visible then behind a digital interface, suggesting these individuals bear a potentially higher risk, of which they are not fully aware of or protected against, when helping patients in dealing with complications or harms resultant from SFs, which extends beyond community pharmacy.

4.3. Implications for policy

The European Falsified Medicines Directive (FMD 2011/62/EC)[31] is designed to eliminate SFs or 'counterfeit' or 'fake' medication from the legitimate supply chain and limit potential risk of harm to the public. While enshrined in law[31], the UK risks not being able to deliver on the FMD directive[1,32]. The UK left the Europe Union on the 31st of December 2020, losing access to the 'national verification system' whereby pharmacy dispensed medicines get verified against a European central database for their authenticity. The single-use verification codes are provided by manufacturers. This process

facilitates recall and quarantine of SFs discovered belatedly, to reduce individual patients harm keeping the wider public safe. Not abiding by the principles of this directive should only be a temporary situation and urgent government action is now needed to facilitate the implementation of this directive. What is unique is that this directive applies in Northern Ireland which is part of the UK. Under the terms of the Northern Ireland Protocol, part of the UK's Withdrawal Agreement with the EU, FMD will still apply in Northern Ireland, for at least four years (until the NI Protocol is due to be reviewed).

In contrary practise, the MHRA encourages companies to retain the tamper evidence technology on packs supplied to the UK. In the interests of public safety, the Government will evaluate the options for a future UK falsified medicines framework, considering the investment already made by stakeholders [1]. The Association of the British Pharmaceutical Industry support this because it affects their licensed medications across territories. They still in practice must comply with these obligations.

Collectively 15,238 units of SFs medicines appear to have been extricated from the legitimate supply chain, with 7 incidences of SF detection in this study (3.37% detection rate) indicating potentially is big gap between infiltration and pharmacist-led detection. This could be due to good resiliency in the supply chain in detection, however, the credibility of the FOI data is unconvincing due to opacity on "units" and numbers across different time frames, though "15,238 units" seems credible at face value. Governance and supply chain control can be further extended by initiating a UK-wide verification database that integrates with the European dataset in such a way that there is live communication between the systems.

The YCR system should be further championed to the public via patient advocates, but this education is wider in scope than what the agency can deliver and needs to be led by the department of education. Pharmacy, medicine and nursing curriculum should be updated with the specific introduction of education on SFs medicines, as per the successful educational pilot by the WHO in African Nations prove the workforce resiliency and capacity in this vein. Ongoing education and training should be provided to registered professionals, not restricted to pharmacists, but including other pharmacy staff e.g., dispensers, technicians and counter assistants within this training.

It is important to consider that with greater public use of online sources of medication, there is a risk that a thriving illegitimate drug market is being established, or at least not eradicated. This itself poses a risk because with time, falsifiers get better at product presentation and means of subverting the legitimate supply chain, further increasing the scope and scale of the potential harm to public health. Potentially legitimate medicines are diverted into the illicit marketplace, where desperate patients seek prescription medications. Such markets have higher auction-prices, attracting sellers who benefit as arbitrageurs (across drugs and currencies), creating shortages in the legitimate supply chain, which is concerning. This would preferentially happen if the drug price in the illicit market (driven by consumer demand potentially for inappropriate use or abuse e.g., addiction, without medical supervision) is higher than the high street. Arbitrageurs maybe 'responsible businesses' in countries where such practices are allowable or unscrupulous individuals. This distinction influences how medicines are handled, stored or become obsolescent while in their ownership. By the time these drugs reach patients, they are potentially SFs.

Legislation: what is clear is that the Directive (FMD 2011/62/EC)[1] does not apply to unregulated medicines that are increasingly proliferating over the internet and through social media as well as the dark Web. There is a strong sense of public outcry at the harms created by these substances and a need

to consider interventions. While overwhelmingly there is evidence in low to middle-income countries of falsification, there is a lack of acknowledgement of the growing illicit use or the use of licensed medication through illicit pathways in UK & Europe. There is a lack of action to combat this phenomenon in a coordinated fashion, other than through this directive, which the UK no longer acts upon. Given Brexit, the UK has experienced some turbulence in drug-sourcing and the Ukrainian crisis via oil prices, which will add to the baseline cost of medicines as a petroleum derivative. Given the geopolitical risks, at different price points they may become indistinguishable from legitimate medication at face value/presentation.

Alprazolam (Xanax®) is a type of benzodiazepine (classified in the UK as a Schedule 4 CD Benz) that was specifically mentioned by survey respondents, which is highly addictive and susceptible to falsification. In February 2019, the Human Medicines Regulations 2012, regulation 226A, introduced the Serious Shortage Protocol (SSP)[31] which does not identify alprazolam as an item in shortage, predominantly due to its low prescription volume. However, it is a growing public health risk reported in media[33], which identifies UK consuming 22% of global alprazolam trades of the highly addictive anti-anxiety medication on the dark web or darknet. Alprazolam (Xanax®) accounted for 50,000 out of 1.5m observed trades on dark web marketplaces in 2017[34]. Further research corroborates this nonmedical use of alprazolam in the UK, which is an emergent issue, more prevalent in younger adults[35] and remains in the UK media as an ongoing concern[36,37]. No reported MHRA or EMA[38] shortages appear in the legitimate supply chain. In such instances, where it is profitable, legitimate drugs enter the elicit supply chain (with the potential for spoilage and become SFs) traded in unregulated markets, potentially feeding corruption and related nefarious activities.

There are several limitations to this study: its small sample size, over representation of male pharmacists (GPhC registrant diversity data[39] on 31 May 2022 show 38,117 (62.3%) female pharmacists, 22,853 (37.4%) male pharmacists,) and sampling across England only. Further work on two factor authentication technologies for physical product like medicines maybe needed[40].

In conclusion, UK patients are more at risk of fake and falsified medicines. Survey data has previously been used to inform health systems planning, epidemiological surveillance and evaluation, which is the intended outcome of this work. Evaluating the real-world effectiveness and safety of medicines is important because its improved transparency, will benefit the research community, medicines regulators, patient care and ultimately improve public health. The UK needs to stand closer to European counterparts, supporting excellence in pharmacovigilance to not just protect public health in the UK, but to engage in a virtuous cycle improving vigilance across Europe and beyond. We cannot wait for threats to become existential before taking corrective actions.

Statements

Declaration of Interests: The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Figure 1 Self-efficacy scale for community pharmacists about their own and other pharmacists' ability to identify and manage SFs.

Figure 2 Major themes on how can falsified medicines reaching the public be reduced.