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Substandard and Falsified Medicine Detection in the Hospital Setting: False quarantine, offline incidents and response times

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Substandard and Falsified Medicine Detection in the Hospital Setting: False quarantine, offline incidents and response times

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Author Contributions: BN was the Principal Investigator (PI) on this study, BN collected data, BN analysed the data and BN wrote the manuscript.

Data statement: Please contact the corresponding author for access to original data.

Abstract

Objectives: To repeat the Naughton et al., 2016 method to assess the technical effectiveness of digital medicine authentication technology in a hospital setting under European Union Falsified Medicines Directive (EU FMD) conditions.

Design: 2,188 medicines were serialised using 2D data matrix labels and introduced into an operational National Health Service (NHS) hospital dispensary. Staff were asked to check medicines for 2D data matrixes and scan those products in addition to their usual medicine preparation and checking processes. Upon scanning 4% of the medicines labelled with a 2D barcode generated a pop-up which identified the medicine as either authenticated elsewhere (falsified), authenticated here, expired or recalled.

Setting: An NHS teaching hospital based in the United Kingdom and the same site as the Naughton et al., 2016 study.

Participants: General Pharmaceutical Council registered accredited accuracy checking technicians and pharmacists

Primary Outcome Measures: Response times, offline issues, false quarantine episodes and workarounds. The EU FMD maximum response time limit is 300 ms.

Results: During the checking stage of medicine preparation, the average response times for medicine authentication in this study was 131 milliseconds (ms). However, 4.67% of attempted authentications experienced offline issues, an increase of 4.23% from the previous study. An increase in offline instances existed alongside an increase in false quarantine.

Conclusions: Digital drug screening has the capability of operating with response times less than the FMD mandated limit of 300 ms. However, there was a raised incidence of offline errors and cases of false quarantine. The practical and legal implications of supplying an SF medicine during offline

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3 periods without prior authentication, or withholding supply until online status
4 resumes, are not yet fully understood.
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11

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13
14
15 The author has no financial interest related to this study to disclose. The
16 content outlined herein represents the individual opinions of the author(s) and
17 may not necessarily represent the viewpoints of their employers. Dr Naughton
18 is a consultant for Solfen Healthcare Limited and conducts consultancy which
19 aims to generate impact from research.
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24 **Article Summary**

25 **Strengths and limitations of this study.**

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- This study is the first of its kind to assess medicines authentication response times, false quarantine and offline incidents.
 - This study demonstrates the effect that offline issues can have on practice.
 - This study could be improved by being performed at multiple sites.

Introduction

There are many definitions of falsified medicines internationally [1–3]. However, the World Health Organisation (WHO) defines falsified medicines as “Medical products that deliberately or fraudulently misrepresent their identity, composition or source”. The WHO defines substandard medicines as “Authorized medical products that fail to meet either their quality standards or specifications or both”. Substandard medicines, for example, may be medicines which originated from a legitimate manufacturer but contain an unintentional “out of specification” error in their production [4].

Examples of SF medicines are usually seen in Low and Middle-Income Countries (LMIC's), and their administration can lead to side-effects, poor treatment outcomes and death [5–8]. However, falsified medicines are not just an issue in LMIC's. There have also been examples of falsified medicines in High-Income Countries (HICs), for example, a falsified version of an anticancer agent Avastin was discovered which contained no active ingredient [9]. Moreover, there were 11 episodes of falsified medicines identified in the UK between 2001 and 2011 and 222 cases of substandard medicines recalled in the UK during the same period [10]; thus supporting the argument that SF medicines affect both LMIC's and HIC's.

There are many emerging international regulations pertaining to the identification of SF medicine. The United States (US) Drug Supply Chain Security Act [1] and the EU Falsified Medicines Directive (EUFMD) [3,11] are the most widely known regulations internationally. The DSCSA relies on a track and trace process where medicines are scanned upon transfer of

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3 ownership while the falsified medicines directive has mandated medicine
4 commission at production and digital drug screening or medicines
5 authentication (MA) at the point of supply to the patient, i.e. an end to end
6 approach. Both regulations aim to identify substandard (recalled and expired)
7 and falsified or counterfeit medicines.
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13 The EU FMD is a pan-European regulation which mandates medicine
14 authentication also known as medicine decommissioning at the point of supply
15 to the patient and involves the scanning of a two-dimensional barcode.
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The data contained within this 2D data matrix is then digitally crosschecked
against a national database to determine whether or not a medicine is recalled,
expired or potentially falsified. The FMD mandated MA approach is an
entirely new process for much of Europe and will affect every pharmacy
throughout the EU. Each European hospital or community pharmacy must be
compliant by February 9th 2019. Although this regulation has been in
existence since 2011, there are low levels of awareness and understanding
amongst practitioners. A publication by Naughton et al. in 2016 [13] identified
issues regarding the relatively poor operational authentication and detection
rate of this approach. Naughton et al., 2016 identified accuracy checking
technicians and pharmacists at the checking stage of medicine supply as the
best-placed personnel within the dispensary to carry out the decommissioning

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3 process, based on scanning compliance data. The authentication technology in
4 the Naughton et al. study did not report offline episodes or false quarantine but
5 did report an average response time of less than 300 ms. However, not all
6 medicines in the Naughton et al. 2016 study were scanned and of those
7 scanned not all were appropriately quarantined in accordance with the study
8 protocol. These results demonstrated a significant operational quality concern
9 with the digital MA approach [13].

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18 A repeat of the Naughton et al. study was undertaken under near-identical
19 conditions with one alteration to the MA technology. This change involved the
20 inclusion of an audio alert, which was suggested by study participants as part
21 of a Delphi method study [14]. This audio alert sounded upon the
22 authentication of a falsified medicine (authenticated elsewhere) or a
23 substandard medicine (expired or recalled). This study generated a wealth of
24 data relating to the incoming digital drug screening approach. The objective of
25 this paper is to assess the technical data gathered in this study. This paper
26 focusses on some of the key FMD parameters, i.e. offline issues, false
27 quarantine and response times and observes the workarounds associated with
28 the new process. The implications of the EU FMD have the potential to be
29 hugely disruptive to healthcare delivery in the face of poor implementation.
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This paper aims to help healthcare providers to understand the potential
technical disruption which may affect medicine supply and patient outcomes.

50 **Methods**

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52 A follow-up study to Naughton et al., 2016 [13] was conducted to gain further
53 understanding of the FMD process from a technical perspective and to identify

the impact of an audio alert at the point of product authentication. This study included multiple objectives, four of which are explored in this paper.

Objectives

- To establish MA technology offline frequency (i.e. how often the system failed to connect to the medicines verification database),
- To identify the frequency of false quarantine in this approach,
- To identify MA response times (i.e. how long it took for the technology to communicate with the database and return a response),
- To observe workarounds associated with the MA approach.

Study Site

This study was performed in the same NHS hospital site that hosted the baseline study by Naughton et al. in 2016, namely Oxford University Hospitals NHS Foundation Trust.

Product Serialisation Method

Medicine product lines were labelled with a pre-programmed two-dimensional barcode sticker (30 product lines in total), twice a week, in the morning and early afternoon for an eight-week period to ensure that medicine lines in the study remained serialised for the duration of the eight-week study, as per the Naughton et al., study in 2016. The pre-programmed 2D barcode sticker identified each product as being ‘authenticated’, ‘already authenticated here’, ‘authenticated elsewhere’ (falsified), ‘product recalled’, ‘batch recalled’ or ‘expired’ at frequencies described in **Table 1.0**.

Table 1.0: A description of each pop-up alert and corresponding frequency throughout the investigated sample.

Popup Message (Colour)	Frequency as a percentage of serialised products entered into
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	the study (n=2,188)
Authenticated (Purple symbol requiring no action)	96%
Already Authenticated here (Amber)	Naturally occurring ¹
Authenticated Elsewhere/Falsified (Amber)	1%
Product Recalled (Red)	1%
Pack Recalled (Red)	1%
Pack Expired (Red)	1%

Medicines with serialised stickers attached were recorded in a database maintained by the PI; these medicine packs were then compared to the medicines quarantined by NHS staff members and those recorded as scanned by the MA provider's database. Not all medicines within the dispensary were serialised to simulate initial FMD decommissioning in a live environment, i.e. medicines manufactured before 2019 will be permitted to be sold without FMD safety features. However, any medicines manufactured beyond February 9th, 2019 will require safety features, resulting in a mix of serialised and non-serialised medicines in the supply chain.

Comparability of Studies

The method used in this study were almost identical to the approach taken in stage one of the Naughton et al. 2016 study (i.e. that medicine decommissioning was performed by pharmacists and accuracy checking technicians at the checking stage). The exception was that the technology including an audio alert which alarmed upon the attempted authentication of a medicine requiring quarantine. The same portfolio of 30 medicine lines was used over an eight-week period, and the participants were given the same

¹ If a medicine were scanned twice, the second scan would generate a pop up which stated that the medicine was 'Already Authenticated Here'. Therefore, these alerts were 'Naturally Occurring' and not introduced by the PI.

presentation and demonstration of the authentication technology as per the protocol, however, despite the best efforts of the PI, there may have been some perceived differences between both studies and these are noted in **Table 2**.

Table 2: Potential differences between Naughton et al. 2016 and the repeat study.

Naughton et al. 2016 (Stage one)	Repeat Study	Considerations
No previous exposure to MA technology	Previous exposure to MA technology	Previous results have not identified an association between technology exposure and increased compliance. There was a greater than a one-year interval between studies
Conducted as a service evaluation study	Conducted as a research study	The repeat study involved ethical approval and written consent
This study was proposed by the Principal Investigator (PI)	The study was based on a consensus improvement (audio alarm) suggested by the participants	Compliance may have been increased by the motivation to implement an idea that was suggested by the participants

Ethical Approvals

This study was classified as research according to NIHR guideline's; Keele University provided ethical approvals. Health Research Authority approvals and Trust R&D approvals were required and provided by both organisations.

Patient and Public Involvement

Patients and the public were not involved in study design or data collection as the research question regarded health information technology within a hospital setting. In this context it had little impact on patients. In a

community setting this technology may have impacted the public to a greater extent and would therefore be warranted.

Results

Naughton et al., 2016 [13] and the repeat study refer to studies carried out in 2015 and 2016 respectively and were each conducted over the same duration, using the same 30 serialised medicines, which explains the similar number of products serialised in each study in **Figure 1.0**.

Figure 1.0: [13].

In Naughton et al. 2016, 2,115 serialised medicines were introduced into an active, operational hospital dispensary 92 of which generated a pop-up requiring medicine quarantine; the repeat study involved a total of 2,188 medicines and of these 89 generated a pop-up identifying the medicine as requiring quarantine. According to protocol participants would then place these products in a quarantine box, away from medicines in circulation within the dispensary.

The EU FMD has mandated a maximum data round-trip (from scanning to external database and back) response rate of less than 300 ms. Across both studies, this has been achieved with a quicker response rate observed in the repeat study. Offline issues, appear to have been more frequent in the repeat study with a 4.23% increase when compared to the Naughton et al. 2016 study. False quarantines were recorded in both studies. A false quarantine refers to when a staff member incorrectly quarantines a medicine. There were 11 cases in 2015 and 37 cases in 2016. The response times and frequency of

offline issues recorded in Naughton et al., 2016 and the repeat study are outlined in **Table 3** below.

Table 3: The response times and frequency of offline issues recorded in Naughton et al. 2016 and the repeat study.

Parameter	Naughton et al., 2016	Repeat Study	Expected Standard
MAT response times	152 ms (n=1604*)	131ms (n=2503*)	300 ms
MAT Offline frequency	0.44% (n=1604)	4.67% (n=2503)	Undefined
*These numbers represent total scans in each study which include decommissions, verifications, duplicate scans and re-commissioning.			

The false quarantine figure for the Naughton et al. 2016 study was extracted from previously gathered unpublished data [13].

False Quarantine and False Negatives

The basis of an effective diagnostic test relies on its sensitivity and specificity. Sensitivity or true positive rate measures the proportion of positives identified as such by the test [15–17]. Specificity or true negatives, report the proportion of negatives that are correctly identified by the test [15–17]. The company providing the solution tested this technology and the PI also performed ad-hoc testing throughout the studies to ensure that medicines with pre-programmed alerts were being delivered to the staff and therefore the technical sensitivity and specificity was accepted as 1.0, granted the technology remained online. This approach is not entirely technical and relies on the interpretation of alerts from the user in a busy environment and the patience of staff to deal with offline issues. **Table 4** identified that the number of false quarantine incidents in the Naughton et al. 2016 study was 11 (of which three occurred during an

offline period). However, there were 37 cases of false quarantine in the repeat study (of which 17 were related to an offline issue). **Table 4.**

Table 4: False quarantine

	Naughton et al., 2016	Repeat Study
False Quarantine	11 (of which three were related to an offline issue)	37 (of which 17 were related to an offline issue)

Workarounds

It was observed during this study that the staff created workarounds. In instances where medicines would not scan, due to an offline issue or otherwise, staff tended to quarantine the product. This workaround demonstrates that the staff erred on the side of caution when faced with offline incidents. It was also observed that after the staff had authenticated a product that was opened and partially used they would use a pen to place across through the 2D data matrix to identify the part pack medicine as already having been authenticated.

Discussion

To knowingly introduce expired, recalled or potentially falsified medicine into the legitimate pharmaceutical supply chain would be disruptive, unethical and compromise patient safety. This study safely assessed the response time, false quarantine frequency and offline frequency in a controlled, operating, closed-loop environment without compromising patient safety and is therefore uniquely positioned. MA has been researched in part, in studies in Belgium where the authentication of medicines has been commonplace [18]. However, there is little evidence which identifies the technical performance of the approach beyond this study.

Response Times

Throughout the Naughton et al. 2016 study and the present repeat study response times of 152 ms and 131ms were observed, respectively. The FMD limit is 300ms. Therefore, both studies are considered within the FMD response time limit.

Workarounds

Work by Debono et al., [19] explains that workarounds were employed to deliver service promptly, and also explained that localised workarounds affect other microsystems [19]. It is important to be aware of and report workarounds. Reporting ensures that ‘What is happening’, and ‘What should be happening’ is understood when making operational decisions which affect microsystems. Awareness of positive workarounds facilitates their incorporation into local policy, and SOPS’s, awareness of negative workarounds allows for their outright and official discouragement. If a culture of reporting workarounds exists within a workplace, workarounds can be acknowledged, and decisions regarding related microsystems and related processes can be made, based on a complete understanding of what is happening in practice.

Bypassing health information systems is common practice in the medical context generally [20] and will become more prevalent as temporary solutions are sought for new and emerging problems with the implementation of novel medicine scanning systems. Kobayashi et al. explains that “Workarounds are a

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3 common technique for dealing with the inherent uncertainty of dynamic work
4 environments” [21]
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8 . The introduction of MA technology in the hospital pharmacy environment
9 brings about a level of inherent uncertainty, and in this study, the uncertainty
10 has demonstrated a specific workaround which involves the crossing through
11 of a 2D barcode rendering it unreadable. According to FMD regulation, a
12 medicine pack requires decommissioning only once, and subsequent supplies
13 from the same pack do not require further verification which makes this
14 workaround a useful approach. However, the destruction of the 2D data matrix
15 removes the opportunity for the hospital to scan that barcode for other
16 practices such as stock taking or medicine verification at the bedside.
17 Hospitals may wish to consider what extra value, beyond FMD compliance,
18 they aim to achieve from serialised medicine packs before allowing or
19 prohibiting a policy of striking through a 2D data matrix.
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35 False Quarantine and Offline Incidents

36 This paper identifies an increase in false quarantine incidents between
37 Naughton et al., 2016 and the repeat study (**Table 3**). The MA was tested
38 before use in each study and ad hoc testing was also performed by the PI,
39 which aimed to identify instances of false negatives and ensure that medicines
40 with pre-programmed alerts were being identified to the staff as such. False
41 negatives were not identified during the testing period. However, there may
42 have been cases where the technology gave no result, e.g. during offline
43 periods. The number of incidences of false quarantine was compared with
44 offline incidents. It is anticipated that the increase in offline issues resulted in
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3 multiple attempts to scan the same medicine which contributed to a higher
4 number of scans in the repeat study (**Table 4**). Staff observations and feedback
5 identified that offline issues resulted in confusion. This confusion is likely to
6 have resulted in the inappropriate quarantine of products (n=37, of which 17
7 were directly related to an offline issue). The effect of offline instances (when
8 the scan from the terminal cannot communicate with the national database) on
9 healthcare institutions may cause a delay in the supply of medicines to
10 patients. This study suggests that an increase in offline issues will increase
11 false quarantine and confusion if adequate support and clear alerts are not
12 provided. An option permitted by the FMD during the offline scenario is to
13 supply a medicine and manually enter the product details to evaluate the
14 provenance of the product when online status resumes or halting medicine
15 supply until the system is again online. Offline issues have a legal and
16 practical impact. Supply without authentication from a professional litigation
17 perspective is not yet apparent; it is currently unclear what would happen in
18 the instance where the technology is offline, resulting in the supply of an SF
19 medicine. Considering there were 222 cases of substandard recalled medicines
20 and 11 cases of falsified medicine in the UK between 2001 and 2011 this
21 scenario is likely to occur sooner rather than later [10]. From a practical
22 perspective, the offline issues seen in this study may result in the cessation of
23 medicine dispensing until online medicine authentication processes resume;
24 for fear of dispensing an SF medicine. This may cause a delay in medicine
25 supply and a backlog of dispensing in pharmacy departments. Pharmacy
26 organisations are suggested to write Standard Operating Procedures (SOP's)
27 which cover their stance on the supply of medicines during offline periods.
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3 Supply without decommissioning could result in a patient receiving an SF
4 medicine, and withholding supply could delay patient treatment or hospital
5 dischargetal.
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9 This study was carried out using a technology provider that had been operating
10 in Greece, Italy and Belgium for approximately ten years. At the time, the
11 offline issues experienced in this study were reported as having affected
12 European clients also. This company is no longer in existence, and national
13 databases will be provided by other companies with less experience in this
14 niche area. There is concern that this level of offline disruption may be
15 repeated and cause the same disruption seen in this study but on a national
16 scale.
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28 **Conclusions and Recommendations**

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30 Response times below 300 ms are realistic and achievable under FMD
31 conditions [13]. Therefore, average response times should not undermine MA
32 compliance. However, offline issues may be linked to false quarantine and are
33 likely to have caused significant delays and confusion during offline periods in
34 the present study. Hospitals and pharmacies are suggested to review their
35 dispensing SOP's to include guidance regarding medicine dispensing during
36 offline periods. Hospitals and community pharmacies could also record offline
37 periods as a risk on their risk registers. However, they could also mandate that
38 their technology providers build in explicitly clear alerts that describe
39 precisely what is required during offline periods and match these alerts with
40 clear internal guidance, Standard Operating Procedures (SOP's) and training.
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42 Although this technological approach has proven its ability to operate at
43 average speeds well below the FMD mandated limit of 300 milliseconds, it is
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3 suggested from this study that offline issues may have an effect on false
4 quarantine and that offline issues are likely to disrupt the delivery of
5 medicines to patients. One way to reduce offline issues would be to penalise
6 the National Medicines Verification System (NMVS) provider for offline
7 instances beyond an agreed contracted level, e.g. 1%. With appropriate
8 incentives, NMVS providers may be more likely to prioritise and rectify
9 offline incidents.
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11 It is important to be aware of the value of medicine serialisation and decide if
12 an organisation wishes to grasp additional value or settle for the minimum
13 level of legal compliance. It is suggested that the General Pharmaceutical
14 Council (GPhC) should also provide clear guidance on the sanctions
15 associated with failure to decommission a medicine according to EU FMD
16 legislation.
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References

1. Research C for DE and. Drug Supply Chain Security Act - Title II of the Drug Quality and Security Act [Internet]. [cited 2017 Feb 24]. Available from: <https://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/ucm376829.htm>
2. European Medicines Agency - Human regulatory - Falsified medicines [Internet]. [cited 2016 Sep 20]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000186.jsp
3. Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal productsText with EEA relevance - dir_2011_62_en.pdf [Internet]. [cited 2016 Jun 9]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf
4. WHO | Definitions of Substandard and Falsified (SF) Medical Products [Internet]. WHO. [cited 2017 Jun 27]. Available from: <http://www.who.int/medicines/regulation/ssffc/definitions/en/>
5. Newton PN, Hanson K, Goodman C. Do anti-malarials in Africa meet quality standards? The market penetration of non-quality-assured artemisinin combination therapy in eight African countries. *Malar J.* 2017;16:204.
6. Nayyar GM, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis.* 2012 Jun 1;12(6):488–96.
7. Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ, Bennish ML. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. *BMJ.* 1995 Jul 8;311(6997):88–91.

8. Renschler JP, Walters KM, Newton PN, Laxminarayan R. Estimated Under-Five Deaths Associated with Poor-Quality Antimalarials in Sub-Saharan Africa. *Am J Trop Med Hyg.* 2015 Jun 3;92(6 Suppl):119–26.
9. Mackey TK, Cuomo R, Guerra C, Liang BA. After counterfeit Avastin®--what have we learned and what can be done? *Nat Rev Clin Oncol.* 2015 May;12(5):302–8.
10. Almuzaini T, Sammons H, Choonara I. Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011). *BMJ Open.* 2013 Jul 1;3(7):e002924.
11. Union PO of the E. Commission Delegated Regulation (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use (Text with EEA relevance) [Internet]. 2015 [cited 2017 Dec 19]. Available from: <https://publications.europa.eu/en/publication-detail/-/publication/645fa920-cef8-11e5-a4b5-01aa75ed71a1/language-en>
12. Naughton BD, Smith JA, Brindley DA. Establishing good authentication practice (GAP) in secondary care to protect against falsified medicines and improve patient safety. *Eur J Hosp Pharm.* 2016 Mar 1;23(2):118–20.
13. Naughton B, Roberts L, Dopson S, Chapman S, Brindley D. Effectiveness of medicines authentication technology to detect counterfeit, recalled and expired medicines: a two-stage quantitative secondary care study. *BMJ Open.* 2016 Dec 1;6(12):e013837.
14. Naughton B, Roberts L, Dopson S, Brindley D, Chapman S. Medicine authentication technology as a counterfeit medicine-detection tool: a Delphi method study to establish expert opinion on manual medicine authentication technology in secondary care. *BMJ Open.* 2017 May 6;7(5):e013838.
15. Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. *Contin Educ Anaesth Crit Care Pain.* 2008 Dec 1;8(6):221–3.
16. Altman DG, Bland JM. Diagnostic tests. 1: Sensitivity and specificity. *BMJ.* 1994 Jun 11;308(6943):1552.
17. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. *Acta Paediatr.* 2007 Mar 1;96(3):338–41.
18. Simoens S. Analysis of Drug Authentication at the Point of Dispensing in Belgian and Greek Community Pharmacies. *Ann Pharmacother.* 2009 Oct 1;43(10):1701–6.
19. Debono D, Greenfield D, Black D, Braithwaite J. Workarounds: straddling or widening gaps in the safe delivery of healthcare. In: Proceedings of 7th international conference in organisational behaviour in health care (OBHC). 2010.

20. Koppel R, Wetterneck T, Telles JL, Karsh B-T. Workarounds to Barcode Medication Administration Systems: Their Occurrences, Causes, and Threats to Patient Safety. *J Am Med Inform Assoc*. 2008 Jul 1;15(4):408–23.
21. Kobayashi M, Fussell SR, Xiao Y, Seagull FJ. Work Coordination, Workflow, and Workarounds in a Medical Context. In: *CHI '05 Extended Abstracts on Human Factors in Computing Systems [Internet]*. New York, NY, USA: ACM; 2005 [cited 2018 Aug 9]. p. 1561–1564. (CHI EA '05). Available from: <http://doi.acm.org/10.1145/1056808.1056966>

Figure 1.0: A diagram identifying the total number of medicines included in both studies [13].

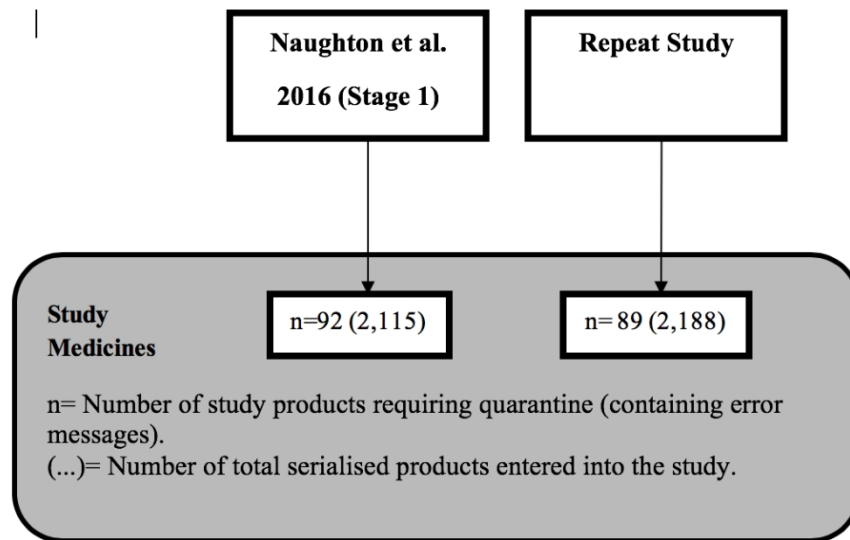


Figure 1.0: A diagram identifying the total number of medicines included in both studies [13].

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Medicine Authentication Technology in Practice: A quantitative study to assess incorrect quarantine, average response times and offline issues in the hospital setting.

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Medicine Authentication Technology in Practice: A quantitative study to assess incorrect quarantine, average response times and offline issues in the hospital setting.

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Abstract

Objectives: To introduce serialised medicines into an active hospital dispensary and assess the technical effectiveness of digital medicine authentication technology under European Union Falsified Medicines Directive (EU FMD) conditions.

Design: Thirty medicine lines were serialised using 2D data matrix labels and introduced into an operational UK National Health Service (NHS) hospital dispensary. Staff were asked to check medicines for 2D data matrixes and scan those products in addition to their usual medicine preparation and checking processes. Four percent of the study medicines were labelled with a 2D barcode which generated a pop-up identifying the medicine as either authenticated elsewhere (falsified), authenticated here, expired or recalled.

Setting: An NHS teaching hospital based in the United Kingdom and the same site as the Naughton et al., 2016 study.

Participants: General Pharmaceutical Council registered accredited accuracy checking technicians and pharmacists

Primary Outcome Measures: Average response times, offline issues, instances of incorrect quarantine and workarounds. The EU FMD maximum response time is 300 milliseconds.

Results: During the checking stage of medicine preparation, the average response time for medicine authentication in this study was 131 milliseconds (ms). However, 4.67% of attempted authentications experienced offline issues, an increase of 4.23% from the previous study. An increase in offline instances existed alongside an increase in incorrect quarantine.

Conclusions: Digital drug screening has the capability of operating with average response times which are below the maximum FMD limit of 300 ms. However, there was an increased incidence of offline errors and cases of incorrect quarantine. The practical and legal implications of supplying an

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3 Substandard or Falsified medicine during offline periods without prior
4 authentication, or withholding supply until online status resumes, are not yet
5 fully understood.
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15 **Competing interests**

16
17
18 The author has no financial interest related to this study to disclose. The
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21 is a consultant for Solfen Healthcare Limited and conducts consultancy which
22 aims to generate impact from research.
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28 **Article Summary**

29 **Strengths and limitations of this study.**

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- This study methodology is the first of its kind to assess medicines authentication average response times, incorrect quarantine and offline incidents within an active healthcare context.
 - This study provides evidence of offline issues and demonstrates the effect that these instances can have on practice.
 - This study identifies the strengths and limitations of medicines authentication technology.
 - This study could be improved by being performed and compared to multiple UK sites.
 - This study could be improved by being repeated in multiple EU countries.

Introduction

There definition of a falsified medicine differs internationally [1–3]. However, the World Health Organisation (WHO) defines falsified medicines as “Medical products that deliberately or fraudulently misrepresent their identity, composition or source”. The WHO defines substandard medicines as “Authorized medical products that fail to meet either their quality standards or specifications or both”. Substandard medicines, for example, may be medicines which originated from a legitimate manufacturer but contain an unintentional “out of specification” error in their production [4].

Instances of Substandard and Falsified (SF) medicines are usually seen in Low and Middle-Income Countries (LMIC's), and their administration can lead to side-effects, poor treatment outcomes and death in already life-threatening conditions such as malaria [5–8]. However, falsified medicines are not just an issue in LMIC's. There have also been examples of falsified medicines in High-Income Countries (HICs), for example, a falsified version of an anticancer agent Avastin was discovered which contained no active ingredient [9]. Moreover, there were 11 episodes of falsified medicines identified in the UK between 2001 and 2011 and 222 cases of substandard medicines recalled in the UK during the same period [10]; thus supporting the argument that SF medicines affect both LMIC's and HIC's.

There are many emerging international regulations pertaining to the identification of SF medicine. The United States (US) Drug Supply Chain Security Act (DSCSA) [1] and the EU Falsified Medicines Directive (EUFMD) [3,11] are the most widely known regulations internationally. The DSCSA relies

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3 on a track and trace process where medicines are scanned upon transfer of
4 ownership while the falsified medicines directive has mandated medicine
5 commission at production and digital drug screening or medicines
6 authentication (MA) at the point of supply to the patient, i.e. an end to end
7 operation. Both regulations aim to identify substandard (recalled and expired)
8 and falsified or counterfeit medicines.
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11 The EU FMD is a pan-European regulation which mandates medicine
12 authentication also known as medicine decommissioning at the point of supply
13 to the patient and involves the scanning of a two-dimensional barcode.
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15 Manufacturers are currently preparing for prescription only medicine (POM)
16 serialisation. Therefore different manufacturers are at different stages of
17 preparedness. Manufacturers must have all of their new products serialised, and
18 dispensers must have operations in place to authenticate (scan) the 2D barcode
19 on each medicine pack dispensed from February 9th 2019 [12]. The data
20 contained within this 2D data matrix is then digitally crosschecked against a
21 national database to determine whether or not a medicine is recalled, expired or
22 potentially falsified. The FMD mandated MA approach is an entirely new
23 process for much of Europe and will affect every pharmacy throughout the EU.
24 Each European hospital or community pharmacy must be compliant by
25 February 9th 2019. Although this regulation has been anticipated since 2011,
26 there are low levels of awareness and understanding amongst practitioners. A
27 publication by Naughton et al. 2016 [13] identified issues regarding the
28 relatively poor operational authentication and detection rate of this approach.
29 Naughton et al., 2016 identified accuracy checking technicians and pharmacists
30 at the checking stage of medicine supply as the best-placed personnel within
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3 dispensary operations to carry out the decommissioning process, based on
4 scanning compliance data. The authentication technology in the Naughton et al.
5 study did not report offline episodes or incorrect quarantine but did report an
6 average response time of less than 300 ms. These results demonstrated a
7 significant operational quality concern with the digital MA approach [13]. The
8 implications of the EU FMD have the potential to be hugely disruptive to
9 healthcare delivery in the face of poor implementation. This paper aims to help
10 healthcare providers to understand the potential technical disruption which may
11 affect medicine supply and patient outcomes.
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25 **Methods**

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27 The data from the Naughton et al. 2016 study was re-examined to identify the
28 incidence of offline errors, and incorrect quarantine. The Naughton et al. 2016
29 study methodology was then repeated under near-identical conditions with one
30 alteration to the MA technology. This change involved the inclusion of an audio
31 alert, which was suggested by study participants as part of a Delphi method
32 study [14]. This audio alert sounded upon the authentication of a falsified
33 medicine (authenticated elsewhere) or a substandard medicine (expired or
34 recalled). This study generated a large data set relating to the incoming digital
35 drug screening approach. The objective of this paper is to assess the technical
36 data gathered in this study and compare it with previously published and
37 unpublished data from the Naughton et al study in 2016. This paper focusses on
38 some of the key FMD parameters, i.e. offline issues, incorrect quarantine and
39 average response times and observes the workarounds associated with the
40 proposed medicine authentication operation. Although the wider study included
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multiple objectives, only the four technical objectives below, are explored in this paper.

Objectives

- To establish MA technology offline frequency from the Naughton et al. 2016 study (i.e. how often the system failed to connect to the medicines verification database) and to repeat the study for comparative purposes,
- To identify the frequency of incorrect quarantine in the Naughton et al. 2016 study and to repeat the study for comparative purposes,
- To identify MA average response times in the repeat study (i.e. how long it took for the technology to communicate with the database and return a response) and to compare this to the published results in Naughton et al., 2016,
- To report and discuss workarounds observed with the MA approach in the Naughton et al. 2016 study and the repeat study.

Study Site

This study was performed at the same NHS hospital site that hosted the baseline study by Naughton et al. in 2016, namely Oxford University Hospitals NHS Foundation Trust.

Product Serialisation Method

Medicine product lines were labelled with a pre-programmed two-dimensional barcode sticker (30 product lines in total), twice a week, in the morning and early afternoon for an eight-week period to ensure that medicine lines in the study remained serialised for the duration of the eight-week study, as per the Naughton et al., study in 2016. The pre-programmed 2D barcode sticker identified each product as being 'authenticated', 'already authenticated here', 'authenticated elsewhere' (falsified), 'product recalled', 'batch recalled' or 'expired' at frequencies described in **Table 1.0**.

Table 1.0: A description of each pop-up alert and corresponding frequency throughout the investigated sample.

Popup Message (Colour)	Frequency as a percentage of serialised products entered into the study (n=2,188)
Authenticated (Purple symbol requiring no action)	96%
Already Authenticated here (Amber)	Naturally occurring ¹
Authenticated Elsewhere/Falsified (Amber)	1%
Product Recalled (Red)	1%
Pack Recalled (Red)	1%
Pack Expired (Red)	1%

Medicines with serialised stickers attached were recorded in a database maintained by the PI; these medicine packs were then compared to the medicines quarantined by NHS staff members and those recorded as scanned by the MA provider's database. Not all medicines within the dispensary were serialised to simulate initial FMD decommissioning in a live environment, i.e. medicines manufactured before 2019 will be permitted to be sold without FMD safety features. However, any medicines manufactured beyond February 9th, 2019 will require safety features, resulting in a mix of serialised and non-serialised medicines in the hospital pharmaceutical supply chain.

Comparability of Studies

The methods used in this study were almost identical to the approach taken in stage one of the Naughton et al. 2016 study (i.e. that medicine decommissioning was performed by pharmacists and accuracy checking technicians at the checking stage). The exception was that the technology included an audio alert

¹ If a medicine were scanned twice, the second scan would generate a pop up which stated that the medicine was 'Already Authenticated Here'. Therefore, these alerts were 'Naturally Occurring' and not introduced by the PI.

which alarmed upon the attempted authentication of a medicine requiring quarantine. The same portfolio of 30 medicine lines was used over an eight-week period, and the participants were given the same presentation and demonstration of the authentication technology as per the protocol. However, despite the best efforts of the PI, there may have been some perceived differences between both studies and these are noted in **Table 2**.

Table 2: Potential differences between Naughton et al. 2016 and the repeat study.

Naughton et al. 2016 (Stage one)	Repeat Study	Considerations
No previous exposure to MA technology	Previous exposure to MA technology	Previous results have not identified an association between technology exposure and increased compliance. There was a greater than a one-year interval between studies
Conducted as a service evaluation study	Conducted as a research study	The repeat study involved ethical approval and written consent
This study was proposed by the Principal Investigator (PI)	The study was based on a consensus improvement (audio alarm) suggested by the participants	Compliance may have been increased by the motivation to implement an idea that was suggested by the participants

Ethical Approvals

This study was classified as research according to NIHR guideline's; Keele University provided ethical approvals. Health Research Authority approvals and Trust R&D approvals were required and provided by both organisations.

Patient and Public Involvement

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3 Patients and the public were not involved in study design or data
4 collection as the research question regarded health information technology
5 within a hospital setting. In this context it had little impact on patients. In a
6 community setting this technology may have impacted the public to a greater
7 extent and would therefore be warranted.
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16 Results

17 This repeat study involved a total of 2,188 medicines and of these, 89 generated
18 a pop-up identifying the medicine as requiring quarantine. [Figure 1.0].
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23 **Figure 1.0:** [13].
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26 The EU FMD has mandated a maximum data round-trip (from scanning to
27 external database and back) response rate of less than 300 ms. Across both
28 studies, this has been achieved with a quicker response time observed in the
29 repeat study [Table 3]. Offline issues, appear to have been more frequent in the
30 repeat study with a 4.23% increase when compared to the unpublished data
31 collected as part of the Naughton et al. 2016 study. Incorrect quarantines were
32 recorded in both studies. An incorrect quarantine refers to when a staff member
33 quarantines a medicine that does not generate an alert pop-up. There were 11
34 cases in 2015 and 37 cases in 2016. The response times and frequency of offline
35 issues recorded in Naughton et al., 2016 and the repeat study are outlined in
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51 **Table 3** below.

52 **Table 3: The average response times and frequency of offline issues**
53 **recorded in Naughton et al. 2016 and the repeat study.**
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55 Parameter	56 Naughton et al., 2016	57 Repeat Study	58 Expected Standard
59 MAT average response times	152 ms (n=1604*)	131ms (n=2503*)	300 ms

MAT Offline frequency	0.44% (n=1604)	4.67% (n=2503)	Undefined
*These numbers represent total scans in each study which include decommissions, verifications, duplicate scans and re-commissioning.			

The offline incidents and incorrect quarantine figures were extracted from unpublished data which was collected as part of the Naughton et al. 2016 project [13].

Incorrect Quarantine and False Negatives

The number of incorrect quarantine incidents from the Naughton et al., 2016 study and the repeat study are displayed in **Table 4**. There were 11 cases in the 2016 study (of which three occurred during an offline period). However, there were 37 cases of incorrect quarantine in the repeat study (of which 17 were related to an offline issue). **Table 4**.

Table 4: Incorrect quarantine

	Naughton et al., 2016	Repeat Study
Incorrect Quarantine	11 (of which three were related to an offline issue)	37 (of which 17 were related to an offline issue)

Workarounds

It was observed during this study that staff created workarounds. In instances where medicines would not scan, due to an offline issue or otherwise, staff tended to quarantine the product. This workaround demonstrates that the staff erred on the side of caution when faced with offline incidents. It was also observed that after the staff had authenticated a product that was opened and partially used they would use a pen to place a cross through the 2D data matrix to identify the part pack medicine as already having been authenticated.

Discussion

To knowingly introduce expired, recalled or potentially falsified medicine into the legitimate pharmaceutical supply chain would be disruptive, unethical and compromise patient safety. This study safely assessed the average response time, the frequency of incorrect quarantine and offline frequency in a controlled, operating, closed-loop environment without compromising patient safety and is therefore uniquely positioned. MA has been researched in part, in studies in Belgium where the authentication of medicines has been commonplace (15). However, there is little evidence which identifies the technical performance of the approach beyond this study. Naughton et al., 2016 [13] and the repeat study refer to studies carried out in 2015 and 2016 respectively and were each conducted over the same duration, using the same 30 serialised medicines, which explains the similar number of products serialised in each study in **Figure 1.0**.

Average Response Times

Medicine dispensing within a large university hospital occurs in stages. Broadly speaking the prescription is clinically screened, it is labelled, it is dispensed and it is checked. An additional step, such as medicine authentication, could have an impact on prescription processing operation and more specifically the total prescription turn-around time. However, in this case we identify that on average communication from a terminal to a national database will not necessarily be a rate limiting step. Throughout the Naughton et al. 2016 study and the present repeat study, average response times of 152 ms and 131ms, respectively, were observed. These two studies provide evidence that the medicine authentication

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3 operation can be performed comfortably within the EU FMD limit of 300 ms,
4 which may reassure UK stakeholders. Although the response times in this study
5 are positive, medicine authentication is not a micro-process which exists in
6 isolation. Instead it should be considered as an additional step which impacts
7 adjacent processes. Therefore, the key to success is not a sub-300 ms response
8 time, but a well thought out re-consideration of current operations in light of
9 this additional step.
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22 Workarounds

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25 Work by Debono et al., (16) explains that workarounds are employed to deliver
26 service promptly, and also explained that localised workarounds affect other
27 microsystems (16). It is important to be aware of and report workarounds.
28 Reporting ensures that “What is happening”, and “What should be happening”
29 is understood when making operational decisions which affect microsystems.
30 Awareness of positive workarounds facilitates their incorporation into local
31 policy, and Standard Operating Procedures (SOPS’s), awareness of negative
32 workarounds allows for their outright and official discouragement. If a culture
33 of reporting workarounds exists within a workplace, workarounds can be
34 acknowledged, and decisions regarding microsystems and related processes can
35 be made, based on a complete understanding of practice. Bypassing health
36 information systems is common in the medical context (17) and will become
37 more common as poorly designed solutions are sought for emerging problems.
38 Kobyashi et al. explains that “Workarounds are a common technique for dealing
39 with the inherent uncertainty of dynamic work environments” (18). The
40 introduction of MA technology and the associated operations in the hospital
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3 pharmacy environment brings about a level of inherent uncertainty, and in this
4 study, this uncertainty has demonstrated a specific workaround which involves
5 the crossing through of a 2D barcode rendering it unreadable, a new
6 phenomenon which was observed consistently across both studies. According
7 to FMD regulation, a medicine pack requires decommissioning only once, and
8 subsequent supplies from the same pack do not require further verification
9 which makes this workaround a useful approach. However, the destruction of
10 the 2D data matrix removes the opportunity for the hospital to scan that barcode
11 for other practices such as stock taking or medicine verification at the bedside.
12 Hospitals may wish to consider what extra value, if any, beyond FMD
13 compliance, they aim to achieve from serialised medicine packs before allowing
14 or prohibiting a policy of striking through a 2D data matrix.

Incorrect Quarantine and Offline Incidents

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17 The basis of an effective diagnostic test relies on its sensitivity and specificity.
18 Sensitivity or true positive rate measures the proportion of positives identified
19 as such by the test (19–21). Specificity or true negatives, report the proportion
20 of negatives that are correctly identified by the test (19–21). However, this
21 approach is not entirely technical and relies on the interpretation of alerts from
22 the user in a busy environment and the patience of staff to deal with offline
23 issues. The MA technology was tested before use in each study and ad hoc
24 testing was also performed by the PI, which aimed to identify instances of false
25 negatives and ensure that medicines with pre-programmed alerts were being
26 identified to the staff as such. False negatives were not identified during the
27 testing period therefore the sensitivity and specificity was deemed to be 100%
28 when the technology was online. However, there may have been cases where
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3 the technology gave no result, e.g. during offline periods. The number of
4 incidences of incorrect quarantine was compared with offline incidents. It is
5 anticipated that the increase in offline issues resulted in multiple attempts to
6 scan the same medicine which contributed to a higher number of scans in the
7 repeat study (**Table 3**). Staff observations and feedback identified that offline
8 issues resulted in confusion. This confusion is likely to have resulted in a higher
9 number of inappropriate product quarantines in the repeat study (n=37, of which
10 17 were directly related to an offline issue). The effect of offline instances
11 (when the scan from the terminal cannot communicate with the national
12 database) on healthcare institutions may cause a delay in the supply of
13 medicines to patients. This study suggests that the increase in offline issues
14 between both studies is responsible for the increased incorrect quarantine rate
15 and confusion, which is likely to be problematic in the face of inadequate
16 support and clear information technology alerts. An option permitted by the
17 FMD during the offline scenario is to supply a medicine and manually enter the
18 product details to evaluate the provenance of the product when online status
19 resumes or halting medicine supply until the system is again online. Offline
20 issues have a legal and practical impact. Supply without authentication from a
21 professional litigation perspective is not yet apparent; it is currently unclear
22 what would happen in the instance where the technology is offline, resulting in
23 the supply of an SF medicine. Considering there were 222 cases of substandard
24 recalled medicines and 11 cases of falsified medicine in the UK between 2001
25 and 2011 this scenario is likely to occur sooner rather than later [10]. From a
26 practical perspective, the offline issues seen in this study may result in the
27 cessation of medicine dispensing until online medicine authentication processes
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3 resumes; for fear of dispensing an SF medicine. This may cause a delay in
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5 medicine supply and a backlog of dispensing in pharmacy departments.
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7 Pharmacy organisations are suggested to write Standard Operating Procedures
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9 (SOP's) which cover their stance on the supply of medicines during offline
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11 periods. Supply without decommissioning could result in a patient receiving an
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13 SF medicine, and withholding supply could delay patient treatment or hospital
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15 discharge.
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19 This study was carried out using a technology provider that had been operating
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21 in Greece, Italy and Belgium for approximately ten years. At the time, the
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23 offline issues experienced in this study were reported as having affected
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25 European clients also. This company is no longer in existence, and national
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27 databases will be provided by other companies with less experience in this niche
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29 area. There is concern that this level of offline disruption may be repeated and
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31 cause the same disruption seen in this study, but on a national scale.
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36 **Conclusions and Recommendations**

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39 Average response times below 300 ms are realistic and achievable under FMD
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41 conditions [13]. Therefore, average response times should not undermine MA
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43 effectiveness. However, offline issues may be linked to incorrect quarantine and
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45 are likely to have caused significant delays and confusion during offline periods
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47 in the present study. Hospitals and pharmacies are suggested to review their
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49 dispensing SOP's to include guidance regarding medicine dispensing operations
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51 during offline periods. Hospitals and community pharmacies could also record
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53 offline periods as a risk on their risk registers. However, they could also
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55 mandate that their technology providers build in explicitly clear alerts that
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57 describe precisely what is required during offline periods and match these alerts
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3 with clear internal guidance, Standard Operating Procedures (SOP's) and
4 training. Although this technological approach has proven its ability to operate
5 at average response times well below the FMD mandated limit of 300
6 milliseconds, it is suggested from this study that offline issues may have an
7 effect on incorrect quarantine and that offline issues are likely to disrupt the
8 delivery of medicines to patients. One way to reduce offline issues would be to
9 penalise the National Medicines Verification System (NMVS) provider for
10 offline instances beyond an agreed contracted level. With appropriate
11 incentives, NMVS providers may be more likely to prioritise and rectify offline
12 incidents.
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26 It is important to be aware of the value of medicine serialisation and decide if
27 an organisation wishes to grasp additional value or settle for the minimum level
28 of legal compliance. It is suggested that the General Pharmaceutical Council
29 (GPhC) should also provide clear guidance on the sanctions associated with
30 failure to decommission a medicine according to EU FMD legislation.
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References

1. Research C for DE and. Drug Supply Chain Security Act - Title II of the Drug Quality and Security Act [Internet]. [cited 2017 Feb 24]. Available from: <https://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/ucm376829.htm>
2. European Medicines Agency - Human regulatory - Falsified medicines [Internet]. [cited 2016 Sep 20]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000186.jsp
3. Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal productsText with EEA relevance - dir_2011_62_en.pdf [Internet]. [cited 2016 Jun 9]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf
4. WHO | Definitions of Substandard and Falsified (SF) Medical Products [Internet]. WHO. [cited 2017 Jun 27]. Available from: <http://www.who.int/medicines/regulation/ssffc/definitions/en/>
5. Newton PN, Hanson K, Goodman C. Do anti-malarials in Africa meet quality standards? The market penetration of non quality-assured artemisinin combination therapy in eight African countries. *Malar J*. 2017;16:204.
6. Nayyar GM, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis*. 2012 Jun 1;12(6):488–96.
7. Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ, Bennish ML. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. *BMJ*. 1995 Jul 8;311(6997):88–91.
8. Renschler JP, Walters KM, Newton PN, Laxminarayan R. Estimated Under-Five Deaths Associated with Poor-Quality Antimalarials in Sub-Saharan Africa. *Am J Trop Med Hyg*. 2015 Jun 3;92(6 Suppl):119–26.
9. Mackey TK, Cuomo R, Guerra C, Liang BA. After counterfeit Avastin®--what have we learned and what can be done? *Nat Rev Clin Oncol*. 2015 May;12(5):302–8.
10. Almuzaini T, Sammons H, Choonara I. Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011). *BMJ Open*. 2013 Jul 1;3(7):e002924.
11. Union PO of the E. Commission Delegated Regulation (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use (Text with EEA relevance) [Internet]. 2015 [cited 2017 Dec 19]. Available from:

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2
3 [https://publications.europa.eu/en/publication-detail/-/publication/645fa920-](https://publications.europa.eu/en/publication-detail/-/publication/645fa920-cef8-11e5-a4b5-01aa75ed71a1/language-en)
4 [cef8-11e5-a4b5-01aa75ed71a1/language-en](https://publications.europa.eu/en/publication-detail/-/publication/645fa920-cef8-11e5-a4b5-01aa75ed71a1/language-en)
5

- 6
7 12. Naughton BD, Smith JA, Brindley DA. Establishing good authentication practice
8 (GAP) in secondary care to protect against falsified medicines and improve
9 patient safety. *Eur J Hosp Pharm*. 2016 Mar 1;23(2):118–20.
- 10
11 13. Naughton B, Roberts L, Dopson S, Chapman S, Brindley D. Effectiveness of
12 medicines authentication technology to detect counterfeit, recalled and expired
13 medicines: a two-stage quantitative secondary care study. *BMJ Open*. 2016 Dec
14 1;6(12):e013837.
- 15
16 14. Naughton B, Roberts L, Dopson S, Brindley D, Chapman S. Medicine
17 authentication technology as a counterfeit medicine-detection tool: a Delphi
18 method study to establish expert opinion on manual medicine authentication
19 technology in secondary care. *BMJ Open*. 2017 May 6;7(5):e013838.
- 20
21 15. Simoens S. Analysis of Drug Authentication at the Point of Dispensing in Belgian
22 and Greek Community Pharmacies. *Ann Pharmacother*. 2009 Oct
23 1;43(10):1701–6.
- 24
25 16. Debono D, Greenfield D, Black D, Braithwaite J. Workarounds: straddling or
26 widening gaps in the safe delivery of healthcare. In: *Proceedings of 7th*
27 *international conference in organisational behaviour in health care (OBHC).*
28 2010.
- 29
30 17. Koppel R, Wetterneck T, Telles JL, Karsh B-T. Workarounds to Barcode
31 Medication Administration Systems: Their Occurrences, Causes, and Threats to
32 Patient Safety. *J Am Med Inform Assoc*. 2008 Jul 1;15(4):408–23.
- 33
34 18. Kobayashi M, Fussell SR, Xiao Y, Seagull FJ. Work Coordination, Workflow, and
35 Workarounds in a Medical Context. In: *CHI '05 Extended Abstracts on Human*
36 *Factors in Computing Systems [Internet].* New York, NY, USA: ACM; 2005 [cited
37 2018 Aug 9]. p. 1561–1564. (CHI EA '05). Available from:
38 <http://doi.acm.org/10.1145/1056808.1056966>
39
- 40
41 19. Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. *Contin Educ*
42 *Anaesth Crit Care Pain*. 2008 Dec 1;8(6):221–3.
- 43
44 20. Altman DG, Bland JM. Diagnostic tests. 1: Sensitivity and specificity. *BMJ*. 1994
45 Jun 11;308(6943):1552.
- 46
47 21. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and
48 predictive values. *Acta Paediatr*. 2007 Mar 1;96(3):338–41.
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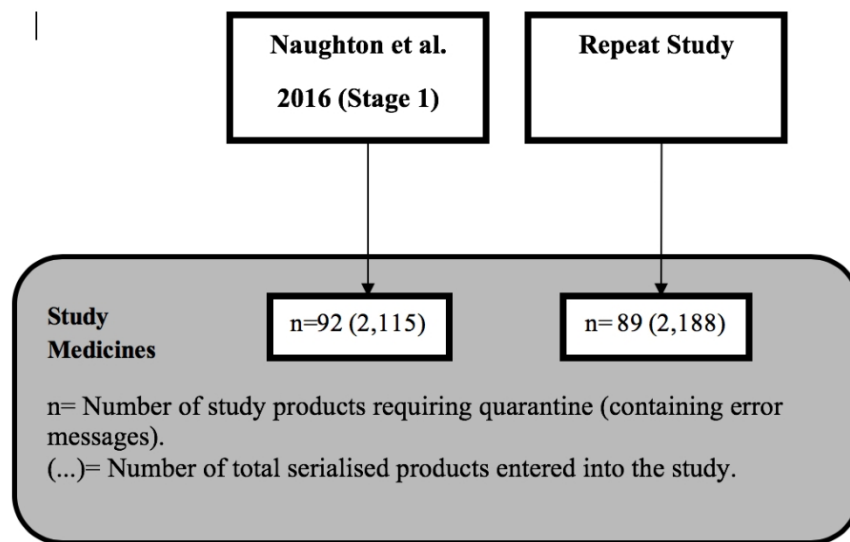


Figure 1.0: A diagram identifying the total number of medicines included in both studies [13].

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Medicine Authentication Technology: A quantitative study of incorrect quarantine, average response times and offline issues in a hospital setting

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Medicine Authentication Technology: A quantitative study of incorrect quarantine, average response times and offline issues in a hospital setting.

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Data statement: Please contact the corresponding author for access to original data.

Abstract

Objectives: To introduce serialised medicines into an active hospital dispensary and assess the technical effectiveness of digital medicine authentication technology under European Union Falsified Medicines Directive (EU FMD) conditions.

Design: Thirty medicine lines were serialised using 2D data matrix labels and introduced into an operational United Kingdom (UK) National Health Service (NHS) hospital dispensary. Staff were asked to check medicines for 2D data matrixes and scan those products in addition to their usual medicine preparation and checking processes. Four per cent of the study medicines were labelled with a 2D barcode which generated a pop-up identifying the medicine as either authenticated elsewhere (falsified), authenticated here, expired or recalled.

Setting: An NHS teaching hospital based in the United Kingdom and the same site as the Naughton et al., 2016 study.

Participants: General Pharmaceutical Council registered accredited accuracy checking technicians and pharmacists

Primary Outcome Measures: Average response times, offline issues, instances of incorrect quarantine and workarounds. The EU FMD maximum response time is 300 milliseconds.

Results: During the checking stage of medicine preparation, the average response time for medicine authentication in this study was 131 milliseconds (ms). However, 4.67% of attempted authentications experienced offline issues, an increase of 4.23% from the previous study. An increase in offline instances existed alongside an increase in incorrect quarantine.

Conclusions: Digital drug screening has the capability of operating with average response times which are below the maximum EU FMD limit of 300 ms. However, there was an increased incidence of offline errors and cases of incorrect quarantine. The practical and legal implications of supplying a

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3 Substandard or Falsified medicine during offline periods without prior
4 authentication, or withholding supply until online status resumes, are not yet
5 fully understood.
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15 **Competing interests**

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18 The author has no financial interest related to this study to disclose. The
19 content outlined herein represents the individual opinions of the author(s) and
20 may not necessarily represent the viewpoints of their employers. Dr Naughton
21 is a consultant for Solfen Healthcare Limited and conducts consultancy which
22 aims to generate impact from research.
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28 **Article Summary**

29 **Strengths and limitations of this study.**

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- This methodology is the first of its kind to assess medicine authentication average response times, incorrect quarantine and offline incidents within an active healthcare context.
 - Evidence of offline issues and their effect on practice is demonstrated in this article.
 - This study identifies the strengths and limitations of medicine authentication technology.
 - As this study was not conducted at multiple hospitals it provides case study evidence only.
 - This research assesses manual medicine authentication and does not provide evidence for automated or robotic dispensing systems.

Introduction

The definition of a falsified medicine differs internationally [1–3]. However, the World Health Organisation (WHO) defines falsified medicines as “Medical products that deliberately or fraudulently misrepresent their identity, composition or source”. The WHO defines substandard medicines as “Authorized medical products that fail to meet either their quality standards or specifications or both”. Substandard medicines, for example, may be medicines which originated from a legitimate manufacturer but contain an unintentional “out of specification” error in their production [4].

Instances of Substandard and Falsified (SF) medicines are usually seen in Low and Middle-Income Countries (LMIC's), and their administration can lead to side-effects, poor treatment outcomes and death in already life-threatening conditions such as malaria [5–8]. However, falsified medicines are not just an issue in LMIC's and examples of falsified medicines exist in High-Income Countries (HICs) also, for example, falsified versions of an anticancer agent Avastin was discovered which contained no active ingredient [9]. Moreover, there were 11 episodes of falsified medicines identified in the United Kingdom (UK) between 2001 and 2011 and 222 cases of substandard medicines recalled in the UK during the same period [10].

Medicine serialisation regulations are emerging internationally. The United States (US) Drug Supply Chain Security Act (DSCSA) [1] and the EU Falsified Medicines Directive (EUFMD) [3,11] are the most widely known. The DSCSA relies on a track and trace process where medicines are scanned upon transfer of ownership while the falsified medicines directive has mandated medicine

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3 commission at production and digital drug screening or medicines
4 authentication (MA) at the point of supply to the patient, i.e. an end to end
5 operation. Both regulations aim to identify substandard (recalled and expired)
6 and falsified or counterfeit medicines.
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12 The EU FMD is a pan-European regulation which mandates medicine
13 authentication also known as medicine decommissioning at the point of supply
14 to the patient and involves the scanning of a two-dimensional barcode.
15 Manufacturers are currently preparing for prescription only medicine (POM)
16 serialisation and are at different stages of preparedness. Manufacturers must
17 serialise products which are manufactured after February 9th 2019, and
18 dispensers must have operations in place to authenticate (scan) the 2D barcode
19 on each medicine pack dispensed from February deadline [12]. The data
20 contained within this 2D data matrix is then digitally crosschecked against a
21 national database to determine whether or not a medicine is recalled, expired or
22 potentially falsified. The FMD mandated MA approach is an entirely new
23 process for much of Europe and will affect every pharmacy throughout the EU.
24 Each European hospital or community pharmacy must be compliant by
25 February 9th 2019. Although this regulation has been anticipated since 2011,
26 there are low levels of awareness and understanding amongst practitioners and
27 a publication by Naughton et al. 2016 [13] identified issues regarding the
28 relatively poor operational authentication and detection rate of this approach.
29 Naughton et al., 2016 identified accuracy checking technicians and pharmacists
30 at the checking stage of medicine supply as the best-placed personnel within
31 dispensary operations to carry out the decommissioning process, based on
32 scanning compliance data. The Naughton et al. study did not discuss offline
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3 episodes or incorrect quarantine but did report an average response time of less
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5 than 300 ms. These results demonstrated a significant operational quality
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7 concern with the digital MA approach [13]. If poorly implemented, the EU
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9 FMD has the potential to be disruptive to healthcare provision. This paper aims
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11 to inform healthcare providers regarding the potential technical disruption
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13 caused by the incoming legislation.
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17 18 **Methods**

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20 Data from the Naughton et al. 2016 study was re-examined to identify the
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22 incidence of offline errors, and incorrect quarantine. The Naughton et al. 2016
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24 study methodology was then repeated under near-identical conditions with one
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26 alteration to the MA technology. This change involved the inclusion of an audio
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28 alert, which was suggested by study participants as part of a Delphi method
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30 study [14]. This audio alert sounded upon the authentication of a falsified
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32 medicine (authenticated elsewhere) or a substandard medicine (expired or
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34 recalled). This study generated a large data set relating to the incoming digital
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36 drug screening approach. The objective of this paper is to assess the technical
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38 data gathered in the wider study and compare it with previously published and
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40 unpublished data from the Naughton et al study in 2016. This paper focusses on
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42 some of the key technical FMD parameters, i.e. offline issues, incorrect
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44 quarantine and average response times and observes the workarounds
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46 associated with the proposed medicine authentication operation. Although the
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48 wider study included multiple objectives, only the three technical objectives
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50 below, are explored in this paper.
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58 **Objectives**

- To establish MA technology offline frequency (i.e. how often the system failed to connect to the medicines verification database) and incorrect quarantine in the repeat study and compare it with previously unpublished data collected as part of the Naughton et al., 2016 study.
- To identify MA average response times in the repeat study (i.e. how long it took for the technology to communicate with the database and return a response) and compare this to the published results in Naughton et al., 2016,
- To observe and discuss workarounds associated with the MA approach in the repeat study and to acknowledge the effect of the audio alert on the technical parameters measured in this study.

Study Site

This study was performed at the same NHS hospital site that hosted the study by Naughton et al. in 2016, namely Oxford University Hospitals NHS Foundation Trust.

Product Serialisation Method

Medicine product lines were labelled with a pre-programmed two-dimensional barcode sticker (30 product lines in total), twice a week, in the morning and early afternoon for an eight-week period to ensure that medicine lines remained serialised throughout the duration of the eight-week study, as per the Naughton et al., study in 2016. The pre-programmed 2D barcode sticker identified each product as being 'authenticated', 'already authenticated here', 'authenticated elsewhere' (falsified), 'product recalled', 'batch recalled' or 'expired' at frequencies described in **Table 1.0**.

Table 1.0: A description of each pop-up alert and corresponding frequency throughout the investigated sample.

Popup Message (Colour)	Frequency as a percentage of serialised products entered into the study (n=2,188)
Authenticated (Purple symbol requiring no action)	96%

Already Authenticated here (Amber)	Naturally occurring ¹
Authenticated Elsewhere/Falsified (Amber)	1%
Product Recalled (Red)	1%
Pack Recalled (Red)	1%
Pack Expired (Red)	1%

Medicines with serialised stickers attached were recorded in a database maintained by the PI; these medicine packs were then compared to the medicines quarantined by NHS staff members and those recorded as scanned by the MA provider's database. Not all medicines within the dispensary were serialised to simulate initial FMD decommissioning in a live environment, i.e. an environment which contains a mix of serialised and non-serialised medicines.

Comparability of Studies

The methodology used in the repeat study were identical to those in stage one of the Naughton et al. 2016 study (medicine decommissioning performed by pharmacists and accuracy checking technicians at the checking stage). However, the technology included an audio alert which alarmed upon the attempted authentication of a medicine requiring quarantine. The same portfolio of 30 medicine lines was used over an eight-week period, and the participants were given the same presentation and demonstration of the authentication technology as per the protocol. Despite the best efforts of the PI, there may have been some perceived differences between both studies and these are noted in

Table 2.

¹ If a medicine were scanned twice, the second scan would generate a pop up which stated that the medicine was 'Already Authenticated Here'. Therefore, these alerts were 'Naturally Occurring' and not introduced by the PI.

Table 2: Potential differences between Naughton et al. 2016 and the repeat study.

Naughton et al. 2016 (Stage one)	Repeat Study	Considerations
No previous exposure to MA technology	Previous exposure to MA technology	Previous results have not identified an association between technology exposure and increased compliance. There was a greater than a one-year interval between studies
Conducted as a service evaluation study	Conducted as a research study	The repeat study involved ethical approval and written consent
This study was proposed by the Principal Investigator (PI)	The study was based on a consensus improvement (audio alarm) suggested by the participants	Compliance may have been affected by the motivation to implement an idea that was suggested by the participants

Ethical Approvals

This study was classified as research according to NIHR guideline's; Keele University provided ethical approvals. Health Research Authority approvals and Trust R&D approvals were required and provided by both organisations.

Patient and Public Involvement

Patients and the public were not involved in study design or data collection as the research question regarded health information technology within a hospital setting. In this context it had little impact on patients.

Results

This repeat study involved a total of 2,188 medicines and of these, 89 generated a pop-up identifying the medicine as requiring quarantine. [Figure 1.0].

Figure 1.0: [13].

The EU FMD has mandated a maximum data round-trip (from scanning to external database and back) response rate of less than 300 ms. Across both studies, this has been achieved with a quicker response time observed in the repeat study [Table 3]. Offline issues, appear to have been more frequent in the repeat study with a 4.23% increase when compared to the unpublished data collected as part of the Naughton et al. 2016 study. Incorrect quarantine was recorded in both studies. An incorrect quarantine refers to when a staff member quarantines a medicine that does not generate an alert pop-up. There were 11 cases in 2015 and 37 cases in 2016. The response times and frequency of offline issues recorded in Naughton et al., 2016 and the repeat study are outlined in **Table 3** below.

Table 3: The average response times and frequency of offline issues recorded in Naughton et al. 2016 and the repeat study.

Parameter	Naughton et al., 2016	Repeat Study	Expected Standard
MAT average response times	152 ms (n=1604*)	131ms (n=2503*)	300 ms
MAT Offline frequency	0.44% (n=1604)	4.67% (n=2503)	Undefined
*These numbers represent total scans in each study which include decommissions, verifications, duplicate scans and re-commissioning.			

The offline incidents and incorrect quarantine figures were extracted from unpublished data which was collected as part of the Naughton et al. 2016 study [13].

Incorrect Quarantine

The number of incorrect quarantine incidents from the Naughton et al., 2016 study and the repeat study are displayed in **Table 4**. There were 11 cases in the

2016 study (of which three occurred during an offline period). However, there were 37 cases of incorrect quarantine in the repeat study (of which 17 were related to an offline issue). **Table 4.**

Table 4: Incorrect quarantine

	Naughton et al., 2016	Repeat Study
Incorrect Quarantine	11 (of which three were related to an offline issue)	37 (of which 17 were related to an offline issue)

Workarounds

It was observed during this study that staff created workarounds. In instances where medicines would not scan, due to an offline issue or otherwise, staff tended to quarantine the product. This workaround demonstrates that the staff erred on the side of caution when faced with offline incidents. It was also observed that after the staff had authenticated a product that was opened and partially used they would use a pen to place a cross through the 2D data matrix to identify the part pack medicine as authenticated.

Discussion

To knowingly introduce expired, recalled or potentially falsified medicine into the legitimate pharmaceutical supply chain would be disruptive, unethical and compromise patient safety. This study safely assessed the average response time, the frequency of incorrect quarantine and offline frequency in a controlled, operating, closed-loop environment without compromising patient safety and is therefore uniquely positioned. Although the addition of the audio alert did not appear to affect the technical parameters measured in this paper i.e. technology response times, false quarantine or offline instances. Further, research is

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3 required to understand the effect of this user instigated alteration on overall
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5 technology use and compliance.
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9 MA has been researched in part, in studies in Belgium where the
10 authentication of medicines has been commonplace [15]. However, there is little
11 evidence which identifies the technical performance of the approach beyond this
12 study. Naughton et al., 2016 [13] and the repeat study refer to studies carried
13 out in 2015 and 2016 respectively and were each conducted over the same
14 duration, using the same 30 serialised medicines, which explains the similar
15 number of products serialised in each study in **Figure 1.0**.
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25 26 Average Response Times

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29 Medicine dispensing within a large university hospital occurs in stages. Broadly
30 speaking the prescription is clinically screened, labelled, dispensed and
31 checked. An additional step, such as medicine authentication, could have an
32 impact on prescription processing operations and more specifically the
33 prescription turn-around time. However, in this case we identify that on average
34 communication from a terminal to a national database will not necessarily be a
35 rate limiting step. Throughout the Naughton et al. 2016 study and the present
36 repeat study, average response times of 152 ms and 131ms, respectively, were
37 observed. These two studies provide evidence that the medicine authentication
38 operation can be performed comfortably within the EU FMD limit of 300 ms,
39 which may reassure UK stakeholders. Although the response times in this study
40 are positive, medicine authentication is not a micro-process which exists in
41 isolation. Instead it should be considered as an additional step which impacts
42 adjacent processes. Therefore, the key to success is not a sub-300 ms response
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3 time, but a well thought out re-consideration of current operations in light of
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5 this additional step.
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10 Workarounds

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13 Work by Debono et al., (16) explains that workarounds are employed to deliver
14 service promptly, and also explained that localised workarounds affect other
15 microsystems (16). It is important to be aware of and to report workarounds.
16 Reporting ensures that “What is happening”, and “What should be happening”
17 is understood when making operational decisions which affect microsystems.
18 Awareness of workarounds generating positive outcomes, facilitates their
19 incorporation into local policy, and Standard Operating Procedures (SOPs)
20 while awareness of workarounds with negative outcomes facilitates their
21 documentation and management . If a culture of reporting workarounds exists
22 within a workplace, workarounds can be acknowledged, and decisions
23 regarding microsystems and related processes can be made, based on a complete
24 understanding of practice.
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42 Bypassing health information systems is common in the medical context [17]
43 and may become more common if digital healthcare systems are not
44 responsibly designed. Kobayashi et al. explains that “Workarounds are a
45 common technique for dealing with the inherent uncertainty of dynamic work
46 environments” [18]. The introduction of MA technology and the associated
47 operations in the hospital pharmacy environment brings about this level of
48 inherent uncertainty, and in this study, this uncertainty has demonstrated a
49 specific workaround which involves the crossing through of a 2D barcode
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3 rendering it unreadable, a new phenomenon which was observed consistently
4 across the study. According to FMD regulation, a medicine pack requires
5 decommissioning only once, and subsequent supplies from the same pack do
6 not require further verification which makes this workaround a useful approach.
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8 However, the destruction of the 2D data matrix removes the opportunity for the
9 hospital to scan that barcode for other practices such as stock taking or medicine
10 verification at the bedside. Hospitals may wish to consider what extra value, if
11 any, beyond FMD compliance, they aim to achieve from serialised medicine
12 packs before allowing or prohibiting a policy of striking through a 2D data
13 matrix.
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Incorrect Quarantine and Offline Incidents

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29 The basis of an effective diagnostic test relies on its sensitivity and specificity.
30 Sensitivity or true positive rate measures the proportion of positives identified
31 as such by the test [19–21]. Specificity or true negatives, report the proportion
32 of negatives that are correctly identified by the test [19–21]. However, this
33 approach is not entirely technical and relies on the interpretation of alerts from
34 the user in a busy environment and the patience of staff to deal with offline
35 issues. The MA technology was tested before use in each study and ad hoc
36 testing was also performed by the PI, which aimed to identify instances of false
37 negatives and ensure that medicines with pre-programmed alerts were being
38 identified to the staff as such. False negatives were not identified during the
39 testing period therefore the sensitivity and specificity was deemed to be 100%
40 when the technology was online. However, there may have been cases where
41 the technology gave no result, e.g. during offline periods. The number of
42 incidences of incorrect quarantine was compared with offline incidents and it is
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3 anticipated that the increase in offline issues resulted in multiple attempts to
4 scan the same medicine which contributed to a higher number of scans in the
5 repeat study (**Table 3**). Staff observations and feedback identified that offline
6 issues resulted in confusion, leading to a higher number of inappropriate product
7 quarantines in the repeat study (n=37, of which 17 were directly related to an
8 offline issue). The effect of offline instances (when the scan from the terminal
9 cannot communicate with the national database) on healthcare institutions may
10 therefore, cause a delay in the supply of medicines to patients. This study
11 suggests that the increase in offline issues is responsible for the increased
12 incorrect quarantine rate and confusion at the point of decommissioning; which
13 is likely to be augmented by inadequately designed information technology
14 alerts. An option permitted by the FMD during the offline scenario is to supply
15 a medicine and manually enter the product details to evaluate the provenance of
16 the product when online status resumes or halting medicine supply until the
17 system is again online. Offline issues have a legal and practical impact. Supply
18 without authentication from a professional litigation perspective is not yet
19 apparent; it is currently unclear what would happen in the instance where the
20 technology is offline, resulting in the supply of an SF medicine. Considering
21 there were 222 cases of substandard recalled medicines and 11 cases of falsified
22 medicine in the UK between 2001 and 2011 this scenario is likely to occur
23 sooner rather than later [10]. From a practical perspective, the offline issues seen
24 in this study may result in the cessation of medicine dispensing until online
25 medicine authentication processes resumes; for fear of dispensing an SF
26 medicine. This may cause a delay in medicine supply and a backlog of
27 dispensing in pharmacy departments. Pharmacy organisations are suggested to
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3 write Standard Operating Procedures (SOPs) which cover their stance on the
4 supply of medicines during offline periods. Supply without decommissioning
5 could result in a patient receiving an SF medicine, and withholding supply could
6 delay patient treatment or hospital discharge.
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12 This study was carried out using a technology provider that had been operating
13 in Greece, Italy and Belgium for approximately ten years. At the time, the
14 offline issues experienced in this study were reported as having affected
15 European clients also. This company is no longer in existence, and national
16 databases will be provided by other companies with less experience in this niche
17 area. There is concern that this level of offline disruption may re-occur and
18 mimic the disruption presented in this study on an international scale.
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30 **Conclusions and Recommendations**

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32 Average response times below 300 ms are realistic and achievable under FMD
33 conditions [13]. Therefore, average response times should not undermine MA
34 effectiveness. However, offline issues may be linked to incorrect quarantine and
35 are likely to have caused significant delays and confusion during offline periods.
36
37 Hospitals and pharmacies are suggested to review their dispensing SOPs to
38 include guidance regarding medicine dispensing operations during offline
39 periods and record offline periods as a risk on their risk registers. They could
40 also mandate that their technology providers build in explicitly clear alerts that
41 describe precisely what is required during offline periods and match those alerts
42 with clear internal guidance, Standard Operating Procedures (SOPs) and
43 training. Although this technological approach has proven its ability to operate
44 at average response times well below the FMD mandated limit of 300
45 milliseconds, it is suggested from this study that offline issues may have an
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3 effect on incorrect quarantine and that offline issues are likely to disrupt the
4 delivery of medicines to patients. One way to reduce offline issues would be to
5 penalise the National Medicines Verification System (NMVS) provider for
6 offline instances beyond an agreed contracted level. With appropriate
7 incentives, NMVS providers may be more likely to prioritise and rectify offline
8 incidents.
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11 It is important to be aware of the value of medicine serialisation and decide if
12 an organisation wishes to grasp additional value or settle for the minimum level
13 of legal compliance. It is suggested that pharmacy regulatory bodies in countries
14 with medicine serialisation legislation, should provide clear guidance
15 concerning the sanctions associated with failure to decommission a medicine
16 according to EU FMD legislation.
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33 Figure 1.0: A diagram identifying the total number of medicines included in
34 both studies
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References

1. Research C for DE and. Drug Supply Chain Security Act - Title II of the Drug Quality and Security Act [Internet]. [cited 2017 Feb 24]. Available from: <https://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/ucm376829.htm>
2. European Medicines Agency - Human regulatory - Falsified medicines [Internet]. [cited 2016 Sep 20]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000186.jsp
3. Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal productsText with EEA relevance - dir_2011_62_en.pdf [Internet]. [cited 2016 Jun 9]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf
4. WHO. Definitions of Substandard and Falsified (SF) Medical Products [Internet]. WHO. [cited 2017 Jun 27]. Available from: <http://www.who.int/medicines/regulation/ssffc/definitions/en/>
5. Newton PN, Hanson K, Goodman C. Do anti-malarials in Africa meet quality standards? The market penetration of non quality-assured artemisinin combination therapy in eight African countries. *Malar J.* 2017;16:204.
6. Nayyar GM, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis.* 2012 Jun 1;12(6):488–96.
7. Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ, Bennish ML. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. *BMJ.* 1995 Jul 8;311(6997):88–91.
8. Renschler JP, Walters KM, Newton PN, Laxminarayan R. Estimated Under-Five Deaths Associated with Poor-Quality Antimalarials in Sub-Saharan Africa. *Am J Trop Med Hyg.* 2015 Jun 3;92(6 Suppl):119–26.
9. Mackey TK, Cuomo R, Guerra C, Liang BA. After counterfeit Avastin®--what have we learned and what can be done? *Nat Rev Clin Oncol.* 2015 May;12(5):302–8.

10. Almuzaini T, Sammons H, Choonara I. Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011). *BMJ Open*. 2013 Jul 1;3(7):e002924.
11. Union PO of the E. Commission Delegated Regulation (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use (Text with EEA relevance) [Internet]. 2015 [cited 2017 Dec 19]. Available from: <https://publications.europa.eu/en/publication-detail/-/publication/645fa920-cef8-11e5-a4b5-01aa75ed71a1/language-en>
12. Naughton BD, Smith JA, Brindley DA. Establishing good authentication practice (GAP) in secondary care to protect against falsified medicines and improve patient safety. *Eur J Hosp Pharm*. 2016 Mar 1;23(2):118–20.
13. Naughton B, Roberts L, Dopson S, Chapman S, Brindley D. Effectiveness of medicines authentication technology to detect counterfeit, recalled and expired medicines: a two-stage quantitative secondary care study. *BMJ Open*. 2016 Dec 1;6(12):e013837.
14. Naughton B, Roberts L, Dopson S, Brindley D, Chapman S. Medicine authentication technology as a counterfeit medicine-detection tool: a Delphi method study to establish expert opinion on manual medicine authentication technology in secondary care. *BMJ Open*. 2017 May 6;7(5):e013838.
15. Simoens S. Analysis of Drug Authentication at the Point of Dispensing in Belgian and Greek Community Pharmacies. *Ann Pharmacother*. 2009 Oct 1;43(10):1701–6.
16. Debono D, Greenfield D, Black D, Braithwaite J. Workarounds: straddling or widening gaps in the safe delivery of healthcare. In: *Proceedings of 7th international conference in organisational behaviour in health care (OBHC)*. 2010.
17. Koppel R, Wetterneck T, Telles JL, Karsh B-T. Workarounds to Barcode Medication Administration Systems: Their Occurrences, Causes, and Threats to Patient Safety. *J Am Med Inform Assoc*. 2008 Jul 1;15(4):408–23.
18. Kobayashi M, Fussell SR, Xiao Y, Seagull FJ. Work Coordination, Workflow, and Workarounds in a Medical Context. In: *CHI '05 Extended Abstracts on Human Factors in Computing Systems* [Internet]. New York, NY, USA: ACM; 2005 [cited 2018 Aug 9]. p. 1561–1564. (CHI EA '05). Available from: <http://doi.acm.org/10.1145/1056808.1056966>
19. Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. *Contin Educ Anaesth Crit Care Pain*. 2008 Dec 1;8(6):221–3.
20. Altman DG, Bland JM. Diagnostic tests. 1: Sensitivity and specificity. *BMJ*. 1994 Jun 11;308(6943):1552.
21. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. *Acta Paediatr*. 2007 Mar 1;96(3):338–41.

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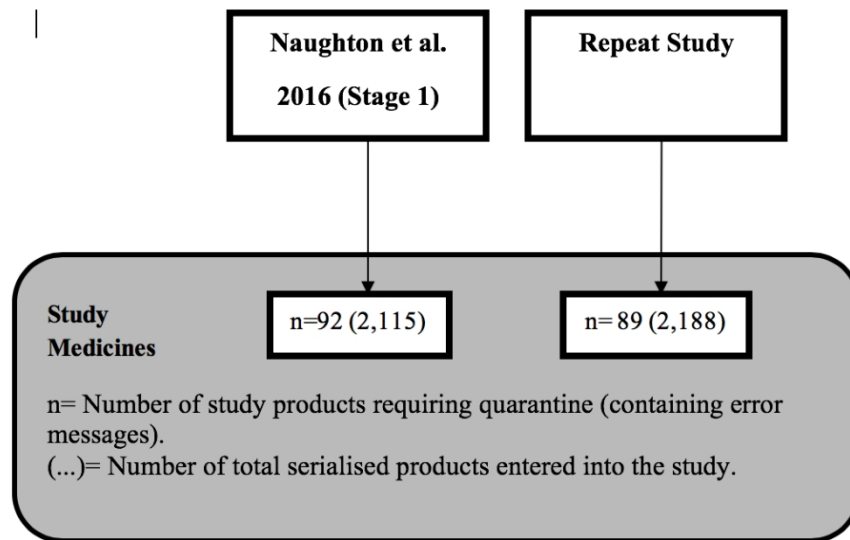


Figure 1.0: A diagram identifying the total number of medicines included in both studies [13].