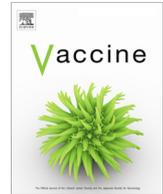




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Commentary

How to ensure we can track and trace global use of COVID-19 vaccines?

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1. Introduction

In response to the devastating SARS-Cov-2 pandemic, an unprecedented surge in vaccine development has occurred. More than 250 vaccines are being developed, at least 50 of which are in clinical trials [1]. Several companies have already started vaccine production ahead of the results of the pivotal Phase III trials. In anticipation of rapid availability of COVID-19 vaccines, shortcuts in the development and regulatory approval processes have been suggested and warned against to combat vaccine hesitancy [2].

Many COVID-19 vaccines are using novel technology platforms little or never used in clinical care previously [1]. Combined with the inherent limited sample size, duration, and population heterogeneity of pre-licensure clinical trials, there is a critical need to monitor safety and effectiveness of the COVID-19 vaccines *post-introduction* [3]. Several COVID-19 vaccines should be available to meet the global need, mostly via COVAX, a new alliance to ensure equitable access [4]. In addition, national mass vaccination programs will be aimed mostly at adults, not children – whom vaccinations traditionally target. Moreover, these programs will likely be conducted in a highly dispersed manner in healthcare institutions, nursing homes, workplaces, schools, etc. . . [5] Sophisticated systems are needed therefore to track and trace on a global scale who was immunized with which COVID-19 vaccine product, where and when. This “exposure” data is vital for any post-introduction study.

2. Key elements for an efficient pharmacovigilance programme

There are two key elements to be considered for an efficient and reliable pharmacovigilance programme

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1) Unique “univocal” identification of vaccines on the global level.

We should be able to reconcile information from various markets on several national drug codes to one global identification number. This will allow us to link diverging brand names to the same vaccine, sharing the same substance(s), dosage form and strength. This is needed to be able to recognise branded variations of the same global vaccine, marketed in different countries. The WHO Competence Centre in Uppsala is specialised in this task and has accepted to adopt the international ISO/CEN standards for the Identification of Medicinal Products (IDMP) for the COVID-19 immunizations.

2) Unique detailed local supply chain identifiers using international standards, that can trace the vaccine from production to point of immunization on the ground.

Barcoding is the current preferred way to meet this need. There are old-fashioned linear barcodes, and the newer two-dimensional (2D) barcodes (Table 1). For conveying labelling information Quick Response (QR) codes are used. But in supply chain management for medicinal products, the dominant standard is using one 2D symbology (GS1 DataMatrix), which should be applied on the secondary packaging (carton boxes), but can also be applied on the primary packaging (vial or prefilled syringe) (Fig. 1). In this issue, Pagliusi et al. successfully piloted such a project with the main Indonesian vaccine manufacturer with a relatively modest level of investment; highlighting a great opportunity to do globally (see below) [6].

This 2D barcode GS1 DataMatrix can be reliably read by dedicated scanners or apps on ubiquitous mobile smartphones [7,8]. This allows more information content density (e.g., vaccine identification, dates of expiration, lot number, serialisation, depending on the packaging level, and the regulatory required label); enables traceability to deter falsification [9]; facilitates documenting patient immunization files; and makes precise product identification possible in reporting adverse events in pharmacovigilance.

Table 1
Description of different barcode technologies and identifiers for medicinal products.

Quick Response (QR) code technology	This graphic 2D barcode embeds a link to websites, to represent text or images (which might include numbers). This can be read and represented by smartphones. It can be created or read by anyone and does not require central control. It has been used in the pharmaceutical area to convey drug and vaccine labelling information in multiple languages.
GS1 Datamatrix	It is a graphical data carrier that represents ASCII characters. The information carried is standardized according global rules defined by GS1 and includes product identification corresponding to the target market of the product. It may also include lot number, expiry date (information from the actual production process, and governed by the manufacturer), and a serial number (a unique, senseless number for each item, guaranteeing the uniqueness of the product package). In the supply chain, the GS1 DataMatrix will use the Global Trade Item Number (GTIN), issued by the Marketing Authorisation Holder or by the Manufacturer. This GTIN will vary by level of packaging and target market (e.g., in the US, it imbeds the National Drug Code). Constant coordination between trading partner's information systems (e.g. wholesalers, community pharmacists) is an essential requirement for the functioning of the supply chain. WHO, UNICEF and others have chosen the GS1 standards as the preferred option to identify products and producers, to avoid falsifications. It is possible to physically scale down this DataMatrix so that it can be printed on the round surfaces of vials or syringes, leaving enough space for the mandatory labelling information.
Pharmaceutical Product Identifier (PhPID)	It is a global number, produced under the ISO/CEN IDMP (Identification of Medicinal Products) standards, under the governance of the WHO Uppsala Monitoring Centre for Global Pharmacovigilance. This PhPID can be mapped at the national level to the National Marketing Authorisation Number (issued by National Competent Authorities) and the GTINs (issued by the companies), who both should keep a public portfolio of identifiers.

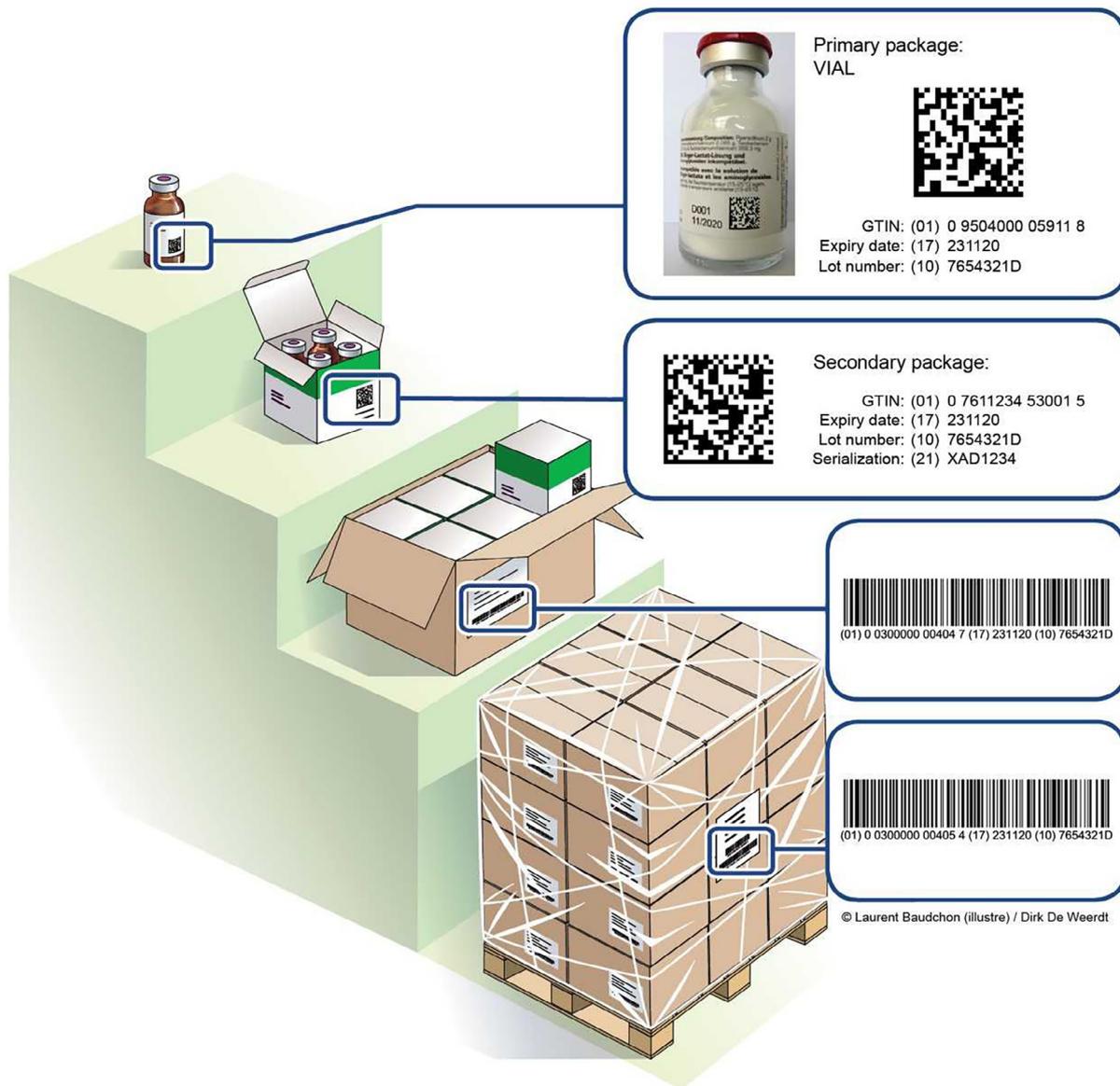


Fig. 1. Representation of Global Trade Item Number, expiry date, lot number and serialisation number on different levels of vaccine packaging with two-dimensional DataMatrix and linear barcode.

Legend: The Global Trade Item Numbers differ on each level of packaging. Expiry date and lot number are the same on each level of packaging. Only the secondary package carries a fourth unique check (the serialisation code as a protection against falsification). Numbers are represented on primary and secondary package by GS1 DataMatrix for dispensing monitoring and by linear barcodes on higher levels of packaging for production and distribution monitoring.

Table 2
Crucial measures to facilitate monitoring of the utilisation of COVID-19 Vaccines.

Measures to be taken	Description
Univocal Global Identification of Covid-19 vaccines	Each uniquely developed vaccine that reaches the market in any country should receive its global univocal identification (named Pharmaceutical Product Identifier or PhPID), as foreseen in the ISO/CEN suite of IDMP standards. This requirement is supported for all medicinal products by the FDA and by EMA, and facilitated by the EU Action Project UNICOM [30,31]. WHO Collaborating Centre for International Drug Monitoring in Uppsala (WHO UMC) is ready to assign such global identification for every unique vaccine.
DataMatrix on the packages, utilizing GS1	National Authorities for marketing authorisation should enforce the presence of scannable 2D barcodes on the primary and secondary packages of vaccines, consistent with CEN ISO/TS 16791, including serialisation (a unique number for every outer package) preferably with GS1. This will enable use of existing systems for falsification and counterfeit protection and facilitate recording of dispensing and administration. Also primary packaging (vials and syringes) should be adequately identified with 2D barcodes (recording the Global Trade Item Number and the batch number). This should not be sacrificed in order to gain cheaper or more rapid market access.
National Immunization Registry	National e-Health systems should adapt their existing immunization registry or create a new registry for COVID-19 vaccines. Registers should be able to collect and record the supply chain identification of the administered vaccines. Open source solutions for database management in national registries can be provided with current programs under the umbrella of GAVI.
Access to Manufacturer traceability data	Companies and national authorities should maintain a publicly available portfolio of identifiers, that consolidates national authorization numbers and supply chain numbers with the univocal global identifiers of all the authorized vaccines. WHO pre-qualification should require, and regulators should request, the printing of supply chain identifiers on the outer packages and vials of the vaccines, also in countries where this is not yet mandatory.
Mandatory recording of immunization acts	Health authorities in the different countries should establish rules to ensure that every act of immunization is recorded, regardless of the way the vaccine was distributed and who administered the vaccine, ensuring patient access to that information, with or without the provision of certificates of immunization. As backup, patients may want to keep a photo of the 2D barcode or label of their COVID 19 vaccine; this may be useful should unexpected long-term adverse events (e.g., enhanced disease) occur.
Apps for vaccine administrators	Certified (preferably open source) apps can be developed to take advantage of the ubiquitous presence of smartphones to allow vaccine administrators (whatever their profession) to record the act of immunization, the date, the patient's ID, and scan the identity of the product. This can result in a certificate for the patient and a recording of the immunization act in the National Vaccination Registry, allowing national and global monitoring of vaccine utilisation. It could also facilitate compliance monitoring when administration must be repeated and protect against hazardous duplicate vaccination with different vaccines. Last but not least, it is a crucial protection against falsified vaccines.
Smooth Pharmaco-vigilance Reporting	The same approach could also facilitate precise identification and effective analysis in case of side-effects to be reported to the global pharmacovigilance monitoring system, or to study comparative effectiveness and safety in big data pharmaco-epidemiological databases.

By capturing product identification, including batch number, from the 2D barcode, quality of reporting improves in the standardized Individual Case Safety Report (ICSR), the basis for global pharmacovigilance.

As the overall immunization schedule has grown globally more complex in the last decades, almost all the key stakeholders in vaccine supply have logically recommended the use of DataMatrix barcodes of GS1: This standard has become the recommended system for trade tracking of health products by WHO [10], and for vaccines, by WHO and the international immunisation consortia [11,12]. It is also advocated by the US Centre for Disease Control [13], USAID [14], the World Bank [15] and the American Academy for Pediatrics [16].

So what is the problem? Hopefully none; we should use COVID-19 as an opportunity globally to modernize the supply chain for vaccines with 2D barcodes with all its benefits for general immunization program improvement, ranging from generating immunization certificates to vaccine uptake monitoring and pharmaco-epidemiology research, to protection against falsified vaccines.

3. Additional actions

But here are few areas where the last mile(s) remain to be crossed with precious little time left:

A. Barcoding the vaccines: Already in 2014, the World Health Organization (WHO) prequalification document [16] first noted the need in next version to recommend GS1 bar codes on all vaccine packaging levels used by manufacturers, except for primary packaging [17]. However, few of the vaccines supplied to low- and middle-income countries (LMIC) via UNICEF currently have 2D barcodes, and probably won't until when it will be required (end of 2021 for vaccines funded by GAVI or 2022 for the vaccines funded by UNICEF) [18]. For COVID-19 vaccines, unfortunately neither the draft WHO prequalification requirements [19] or vaccine

safety surveillance manual [20] mentions 2D barcodes. A UNICEF-led consultation with industry on Sept. 29, 2020 did agree for COVID-19 tenders to list 2D barcodes as "preferred (vs. required) characteristics" on the secondary packaging [21]. The VIPS Alliance (Vaccine Innovation Prioritisation Strategy) advocates in addition the printing of GS1 DataMatrix on the primary packaging [22]. Based on the successful pilot in Indonesia, the Developing Countries Vaccines Manufacturing Network (DCVMN) is ready to expand with funding support [6]. Furthermore, the WHO in a consultation with the industry on November 12, 2020 only proposed the use of QR codes as optional for primary and secondary packaging, or for conveying label information [23].

As COVID-19 vaccine will likely be pioneering the introduction of these new technologies into the complex immunization ecosystem, challenges should be planned for. The minimum requirement for now should be a DataMatrix with the Global Trade Item Name (GTIN) and the batch number and the expiry data and (if possible) the serialisation number on the secondary packages, and a DataMatrix (at first possibly only with the GTIN) on the primary package and the batch number (the vial or prefilled syringe). Since most High Income Country (HIC) developers already routinely apply barcodes to their primary packaging for non-Covid vaccines, we recommend them also doing so for their Covid vaccines shipped to Low and Middle Income Countries (LMIC). Other developers should consider doing so wherever possible, even though this exceeds the minimal preference standards set by WHO/UNICEF. If barcodes are only available for secondary packaging for a developer, this may be bulky (hundreds of doses) and its location will vary. The developer will need to highlight the location of the DataMatrix barcode in the training material and shipment. Each immunization site will also need to adapt its processes to ensure the capture of the barcode data for each vaccinee accurately, knowing this is a system potentially at great risk for error with little backup (e.g., no way for vaccinee to take a photo of primary packaging).

B. Digital Immunization Certificates and National Immunization Registry: Barcode is a digital solution that allows a digital database to document each immunization act. At least two groups [24,25] are developing a digital global COVID-19 immunization certificate. These projects require precise identification of the vaccines. Countries need National Immunization Registries for the imminent wave of COVID-19 immunization campaigns. Many but not all high-income countries already have them, but usually not for adults. Poor integration by ambulatory electronic health record (EHR) software has been a hurdle to adoption of barcodes in the US [26]. For LMICs, open source immunization information systems exist and are already installed in parts of 30 countries [27]; but more than 100 have yet to start. The “digital divide” – in terms of unreliable electricity or inadequate digital data storage– is a major challenge, both within and across nations. Realistically, this problem is unlikely to be solved before planned COVID-19 vaccinations begin in LMIC’s. Therefore, provisions for non-digital alternatives to tracking COVID-19 vaccines will be needed.

C. Explicit policy: The guidance for oversight of COVID 19 vaccines by regulators and WHO, grouped in the ICMRA (International Coalition of Medicines Regulatory Authorities) does not currently clearly address the problem of vaccine identification [28]. The EU Covid-19 Vaccine Strategy mentions flexibility in labelling and packaging, which may be worrying if proper barcoding is not required at the same time [29]. It is not clear to what extent COVID-19 vaccine manufacturers are already taking preparations to make sure all their vaccines shipped include 2D barcodes. Marketing authorisation authorities in Europe have received requests for exemptions to print barcodes on the packaging. Hopefully, the pharmaceutical companies will continue to apply correct identification of their products by printing barcodes on the packaging. Strict guidance from WHO, UNICEF, FDA, EMA, and other national competent authorities is needed. Otherwise, we may face considerable public dismay (and even wrath) re: our inability to track the safety profile of individual Covid-19 vaccines.

In Table 2, we list the essential policy measures needed to permit global monitoring of COVID-19 vaccine utilisation, safety and effectiveness. Undoubtedly each issue will have its own set of hurdles.

The clock is ticking. Let’s act jointly to prepare for this last but vital aspect in the control of the pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Christian Hay is a consultant to GS1.

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