QualityAssessmentofDriedBloodSpotsfromPatientsWith Tuberculosis from 4 Countries

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Quality Assessment of Dried Blood Spots from Patients With Tuberculosis from 4 Countries

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Background: Dried blood spot (DBS) sampling is a blood collection tool that uses a finger prick to obtain a blood drop on a DBS card. It can be used for therapeutic drug monitoring, a method that uses blood drug concentrations to optimize individual treatment. DBS sampling is believed to be a simple way of blood collection compared with venous sampling. The aim of this study was to evaluate the quality of DBSs from patients with tuberculosis all around the world based on quality indicators in a structured assessment procedure.

Methods: Total 464 DBS cards were obtained from 4 countries: Bangladesh, Belarus, Indonesia, and Paraguay. The quality of the DBS cards was assessed using a checklist consisting of 19 questions divided into 4 categories: the integrity of the DBS materials, appropriate drying time, blood volume, and blood spot collection.

Results: After examination, 859 of 1856 (46%) blood spots did not comply with present quality criteria. In 625 cases (34%), this was due to incorrect blood spot collection. The DBS cards from Bangladesh, Indonesia, and Paraguay seemed to be affected by air humidity, causing the blood spots not to dry appropriately.

Conclusions: New tools to help obtain blood spots of sufficient quality are necessary and environmental specific recommendations to determine plasma concentration correctly. In addition, 3% of the DBS cards were rejected because the integrity of the materials suggesting that the quality of plastic ziplock bags currently used to protect the DBS cards against contamination and humidity may not be sufficient.

Key Words: DBS, TB, quality, TDM, plasma concentrations

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BACKGROUND

Tuberculosis (TB) is a disease that continues to affect people all around the world. In 2017, 6.4 million new TB cases were reported.[1] Bangladesh and Indonesia combined made up 19% of all incident TB cases in 2017.[1] Drug-susceptible TB is treated with the first-line anti-TB drugs isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampicin for another 4 months, leading to successful outcomes in 82% of the cases.[1,2] To optimize TB treatment in patients responding poorly to standard treatment or with risk factors for low drug exposure, therapeutic drug monitoring (TDM) can be performed.[3,4] TDM was recently recommended in the TB treatment guidelines of the ATS/CDC/IDSA.[5] One of the barriers to introduce TDM at a large scale is the stability of plasma or serum samples. This can be overcome by implementing dried blood spot (DBS) sampling.[6] This procedure uses a single drop of blood on special absorbent paper to determine the blood drug concentration. DBS has several other advantages, such as easy sample collection and shipment through regular mail, which saves costs for shipment on dry ice.[7] Also, DBS minimizes the biohazard risk due to the use of dried samples, which is a major advantage in countries with a high

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prevalence of HIV coinfection.[6,7] The small sample volume of 20–100 μL blood is a major advantage compared with the 4–10 mL of venous blood collected for conventional blood sampling, making this method suitable for children,[7] but also for those who oppose to large volume venous blood sampling.

There are 2 DBS sampling methods: The first method involves letting the blood drop fall directly within the premarked circle, followed by partial spot analysis. The second method requires the application of the required blood volume by capillary or pipette onto the DBS card, followed by full-spot analysis.[7] The first method is often preferred because it can be performed by untrained personnel but inaccurate sampling may influence analytical results.[8]

Although preliminary results are promising, some hurdles still need to be overcome before DBS sampling can be implemented in TB programs.[9] Laboratories need to clinically validate DBS methods comparing venous samples with fingerprick samples to be able to offer a range of assays. Hematocrit has shown to be of influence on analytical results and should therefore be included during clinical validation.[10–12] Health care workers have to get familiar with the sampling procedure, and pitfalls need to be examined.

The aim of this study was to assess, using a structured checklist, whether DBSs of sufficient quality can be obtained with limited training and to give recommendations on how to improve the quality of DBS samples.

MATERIALS AND METHODS

Data Sets

Feasibility of DBS was evaluated in 5 different settings: International Centre for Diarrhoeal Disease Research in Bangladesh, Grodno Oblast Clinical Centre "Ftiziatria" in Belarus, Lung Hospital Respira, Yogyakarta in Indonesia, Instituto Nacional de Enfermedades Respiratorias y del Ambiente Juan Max Bohener in Paraguay, and Indigenous Hospital of Limpio in Paraguay. Health care workers received DBS packages containing an instruction form, a patient letter, a request form, Whatman FTA DMPK-C DBS cards, plastic ziplock bags to store and ship the cards, desiccant sachets to be included in the ziplock bag for storage and shipment, and lancets to puncture the finger. As DBS sampling was considered to be a simple procedure, health care workers only received written instructions and an instruction video in English.[13,14] DBS samples were collected from patients with TB receiving standard first-line anti-TB treatment. Ethical clearance was obtained at all sites, and patients gave written informed consent.

Validity of the DBS Cards

DBS cards, containing 4 blood spots, were scored on 4 categories: integrity of the DBS materials, appropriate drying time, blood volume, and blood spot collection. The aspects that a DBS card has to comply with for an accurate analysis were based on the "Blood Collection and Handling—Dried Blood Spots" manual of the World Health Organization (WHO).[15,16] For the category integrity of the DBS materials, the plastic ziplock bags were checked if the bag was sealed and had maintained its integrity (holes and rips). Also, the DBS card itself was checked for folds or rips.

For the next category, drying of the DBS card was examined. The card should not be put in the ziplock bag before it was laid to dry for at least half an hour at room temperature in a nonhumid environment avoiding direct sunlight. The inside of the ziplock bag and the outer surface of the desiccant sachet were inspected for blood stains. DBS cards that have not been dried long enough show blood spots of a lighter color.[15]

We also assessed whether a 3-, 5-, or 8-mm punch could be made without punching the ink from the predefined circle. In addition, we examined if the blood spot was consisting of a single drop of blood or multiple overlaying drops.

For the last category, blood spot collection, we examined if the blood spot was collected appropriately, without touching the paper and without using a capillary. This was assessed by judging the shape and consistency of the blood spot. We also looked for the presence of a light ring around the blood spot, which can result from squeezing the blood from the finger.

For each category, a series of questions have been included in a checklist (see **Supplemental Digital Content 1**, http://links.lww.com/TDM/A345). The DBS cards were accepted for analysis if at least 2 blood spots complied with all quality requirements. Two spots will enable a second analysis if something went wrong during sample processing, to confirm the results from the first DBS and to allow different sample preparations to be performed for different assays.[17]

The checklist was filled in for all DBS cards by 2 independent DBS experts: M.A.Z. and H.V. Disagreements were solved by consensus. If the integrity of the DBS materials was compromised or if the drying time was disputable, all 4 DBSs were rejected for analysis. For the other 2 categories, the DBSs were scored individually.

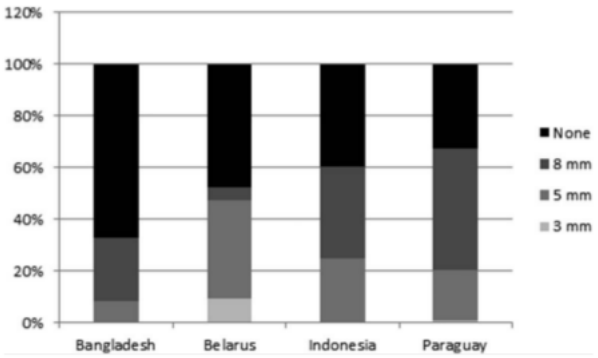

FIGURE 1. The DBSs per country and per punch size. This figure shows how many DBSs could be punched and with which minimum size. If a DBS could be punched with an 8-mm puncher, then it is part of the percentage that could be punched with an 8-mm puncher and not with a 5- or 3-mm puncher.

RESULTS

In total 464 DBS cards with 4 blood spots from 4 countries were assessed; 117 from Bangladesh, 90 from Belarus, 129 from Indonesia, and 128 from Paraguay. The amount of blood spots that could be analyzed based on punch size per country is shown in Figure 1. Rejection rate of the DBSs ranged from 13% for Indonesia, 20% for Paraguay, 37% for Belarus to 52% for Bangladesh. Overall, 46% of all DBSs could not be used according to the predefined criteria for analysis.

Most DBSs could be punched with an 8-mm puncher. This was not the case for the blood spots from Belarus. Only 5% of the blood spots were of sufficient size to be punched with an 8-mm puncher, 43% with a 5-mm puncher, and 52% with a 3-mm puncher.

In Figure 2, the amount of DBSs that were rejected based on 4 categories is shown. DBS cards could not be analyzed in 3% of the 464 cases because of the integrity of the materials. Only for the DBS cards from Indonesia, this did not pose a problem. In Indonesia, different bags, foil barrier ziplock bags (Whatman, 10534321; GE Healthcare, Little Chalfont, United Kingdom), were used instead of the provided plastic ziplock bags. As can be seen in Table 1, the biggest issues were due to the plastic bag being open or a missing sachet with desiccant. On 6 DBS cards from Indonesia, a fungus, typed as *Aspergillus* species, was present. Also, the bags from Indonesia contained 3 DBS cards, only separated by filter papers, whereas there should only be 1 card included per bag.

The second most important reason for the rejection of DBSs was insufficient drying time before placing the DBS cards in the ziplock bag. As can be seen from Table 1 and Figure 2, this problem was most apparent for the DBSs from Bangladesh and Indonesia.

The biggest cause of rejection was inaccurate blood spot collection. The DBS cards were mostly rejected because of contamination of the DBSs, caused by touching the card with either a finger or a capillary. The latter could be recognized by small round circles on the filter paper. A total of 15% of the DBSs from Bangladesh were rejected for touching of the card; however, an additional problem here was the formation of light rings. This eventually caused 58% of the blood spots from Bangladesh to be rejected. For the blood spots from Indonesia, the main issue was that 13% of the spots consisted of multiple overlaying drops of blood. Besides contamination, blood spot volume was an important reason for rejection in Belarus and Indonesia (Fig. 2). This low blood volume caused the blood to not soak through the filter paper of the DBS card, as can be seen in the low percentage stated in Table 1.

Keeping all criteria in mind, an average of 65% of the DBS cards could be used. For Bangladesh, this was only 40%, for Belarus 59%, for Indonesia 80%, and for Paraguay 77% (Fig. 3).

DISCUSSION

Ultimately, the goal is to implement DBS sampling for TDM of anti-TB drugs, to provide a more patient-friendly way of sampling in remote settings. DBS sampling can also be used in other infectious diseases such as HIV, for which not only plasma concentrations of antiretroviral drugs can be determined with DBS, but also viral load.[18] Unfortunately, 46% (859/1856) of the spots in our study were rejected based on strict criteria, leading to an average of 65% of DBS cards that could be used. The high rejection rate of samples in our study showed that DBS sampling would require more training to produce bloods spots of sufficient quality to be analyzed. This confirms the study of Hoogtanders et al which showed that DBSs of sufficient quality for analysis could not be obtained with the first method, which is letting the blood drop fall directly onto the DBS card, without appropriate training.[8,19] This article can help guide health care workers and researchers to collect DBSs of sufficient quality.

We found that the currently used plastic ziplock bags were not of sufficient quality to protect the DBS card from damage, with around 3% of the bags being torn and 4% being open or missing a desiccant sachet. The reason for an open ziplock back, next to opening during transport, could also be because they are difficult to close. In Indonesia, different bags were used, which were of thicker material. These light protected seal bags did not have any problems as far as opening or ripping and could therefore be a better option. A fungus was found on 6 DBS cards, likely caused by

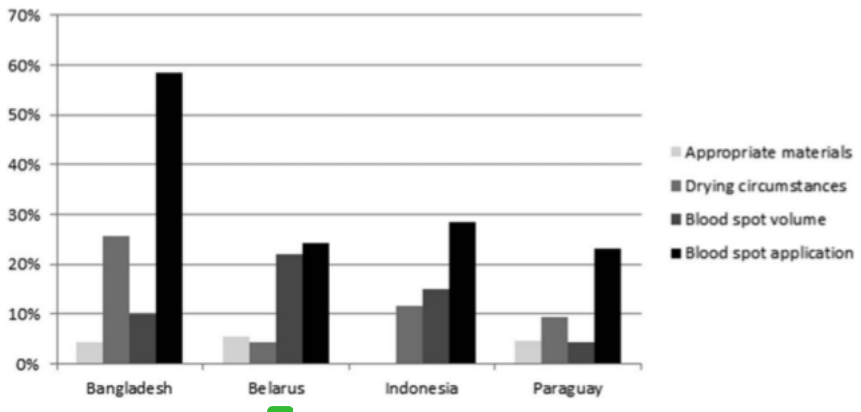

FIGURE 2. Percentage of DBSs that were rejected, divided in 4 categories. The results are shown for the 4 categories separately and not as overall results. One DBS can be part of multiple categories.

TABLE 1. Percentage of DBS Cards That Could be Used per Question From the Checklist

Category	Question	Bangladesh, % N = 117 DBS Cards With 4 Blood Spots	Belarus, % N = 90 DBS Cards With 4 Blood Spots	Indonesia, % N = 129 DBS Cards With 4 Blood Spots	Paraguay, % N = 128 DBS Cards With 4 Blood Spots	Overall, %
Integrity of the DBS materials	In bag with desiccant	95	87	100	98	96
	Bag intact	97	96	100	95	97
	DBS card intact	98	100	100	98	99
Appropriate drying time	Only blood on the DBS card	76	96	88	92	88
	No lighter color blood spots	99	99	100	100	100
Blood volume	One drop of blood	93	98	87	97	94
	Blood soaked through filter paper	96	80	95	98	93
Blood spot collection	Separate blood spots	99	100	100	100	95
	DBS card not touched during application	85	76	77	83	83
	No light rings around the blood spot	55	100	92	92	73

contamination of the DBS cards or filter papers dividing the DBS cards, since the fungus is commonly found on skin. This warrants further study to exclude that the bag itself aided the growth of the fungus. If this is not the case, light protected biohazard seal bags are preferred over the currently used plastic ziplock bags. A study by Winter et al showed that the analysis results were affected by many contaminants, that is, feces, disinfectants, and urine,[20] showing the need for hygiene when performing DBS sampling.

We also assessed whether punches could be obtained without ink from the premarked circle. As it is not known what influence the ink has on the outcome of the analysis, we have decided to reject blood spots that could only be obtained with ink. This was only the case for blood spots that could be obtained with an 8-mm puncher; therefore, it had no influence on the amount of blood spots that could ultimately be analyzed.

Drying conditions was shown to be one of the most important reasons for the rejection of samples from Bangladesh, Paraguay, and Indonesia. Light rings were also more common in these countries, for example, for Bangladesh, 45% of the blood spots needed to be rejected because of this (Table 1). Because the light rings were more common in these countries, it is more likely that a high humidity is the cause of the light rings instead of squeezing of the finger. A high humidity requires a longer drying time.[21] It could also be that the DBS cards were humid before use because the DBS cards were not stored in a plastic ziplock bag with a desiccant sachet before use and were therefore not protected against humid conditions.[22] To prevent this from happening, DBS sampling should be performed in a temperature- and humidity-controlled environment. DBS sampling is not a viable option in remote settings with high humidity or home sampling. An alternative could be to store the DBS cards in a box or package with desiccant sachets. In such an environment, storage of the collected sample can also be done in the box. It needs to be tested whether this would improve drying of the samples.[23]

DBS sampling can be difficult in case of callous skin. Callous skin is difficult to penetrate with the lancet causing issues with obtaining enough blood for the DBS sampling. This was seen for blood spots from Belarus, as the blood

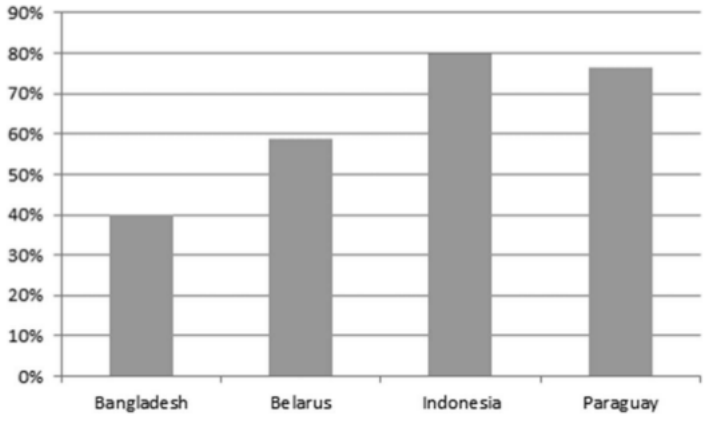

FIGURE 3. Percentage of DBS cards that could be used per country. The percentage of DBS cards that could be used for analysis based on the need for 2 DBSs per DBS cards for analysis.

spots were too small. Use of another type of lancet or an alternative sampling position compared with the finger, that is, the ear lobe, could solve this problem.

A study by Martial et al[24] showed that DBS sampling would not only be more patient-friendly, but also cost-effective, if it could be performed at home. Without practical training, it is shown to be difficult to obtain a blood spot from which the drug concentration can be accurately determined. As TDM for the optimization of TB treatment will likely be performed using 2–4 rounds of TDM,[25,26] it will be easier and more cost-effective to train health care workers instead of patients. Because patients with TB visit the public health service regularly, the DBS sampling could be performed during a scheduled visit. Based on the results from this study, the instructions need to be amended. Instructions could also be made available in native languages to overcome interpretation issues.

CONCLUSIONS

More practical training is needed to adequately perform DBS sampling. Compliance with storage and shipment conditions is important to have the DBS sample arrive in the laboratory and pass quality checks.

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