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ORIGINAL ARTICLE

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A novel syphilis *Treponema pallidum* lipoprotein peptide antigen diagnostic assay using red cell kodecytes in routine blood centre column agglutination testing platforms

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Abstract

Background and Objectives: The detection of treponemal antibodies, which are used to make a diagnosis of syphilis, is important both for diagnostic purposes and as a mandatory blood donor test in most countries. We evaluated the feasibility of using Kode Technology to make syphilis peptide red cell kodecytes for use in column agglutination serologic platforms.

Materials and Methods: Candidate Kode Technology function-spacer-lipid (FSL) constructs were made for the *Treponema pallidum* lipoprotein (TmpA) of *T. pallidum*, using the peptide and FSL selection algorithms, and then used to make kodecytes. Developmental kodecytes were evaluated against a large range of syphilis antibody reactive and non-reactive samples in column agglutination platforms and compared against established methodologies. Overall, 150 reactive and 2072 non-reactive Syphicheck assay (a modified *T. pallidum* particle agglutination) blood donor samples were used to evaluate the agreement rate of the developed kodecyte assay.

Results: From three FSL-peptide candidate constructs, one was found to be the most suitable for diagnostics. Of 150 Syphicheck assay reactive samples, 146 were TmpA–kodecyte reactive (97.3% agreement), compared with 58.0% with the rapid plasmin reagin (RPR) assay for the same samples. Against the 2072 expected syphilis non-reactive samples the agreement rate for TmpA–kodecytes was 98.8%.

Conclusion: TmpA–kodecytes are viable for use as cost-effective serologic reagent red cells for the detection of treponemal antibodies to diagnose syphilis with a high level of specificity in blood centres. This kodecyte methodology also potentially

allows for introduction of the reverse-algorithm testing into low-volume laboratories, by utilizing existing transfusion laboratory infrastructure.

Keywords
blood safety, infectious disease, novel diagnostic assay, syphilis resurgence, *Treponema pallidum*

Highlights

- TmpA–kodecytes are modified reagent red cells suitable for the detection of treponemal antibodies in routine column agglutination testing platforms.
- TmpA–kodecytes have a much higher level of agreement (97.3%) for modified *T. pallidum* particle agglutination-defined reactive samples, in contrast to 58.0% by rapid plasma reagin testing.
- The cost of the function-spacer-lipid-TmpA1 constructs per assay volume of TmpA–kodecytes is 1 US cent.

INTRODUCTION

Syphilis is caused by the spirochete *Treponema pallidum* and is a sexually transmitted disease [1]. Today, although the incidence of transfusion-transmitted syphilis is extremely rare, primarily due to the shift to the use of refrigerated blood and blood components, the possibility for transfusion-transmitted syphilis may still remain for several days after 72 h of cold storage [2–4]. In addition, it is anticipated that the blood donors donated in the acute stage of their infection have a high potential to transmit syphilis by transfusion because they might have active and infectious treponemas in their blood, which often remain undiagnosed on immuno-serology-based screening assays. Furthermore, the US Food and Drug Administration and the World Health Organization (WHO) state that syphilis testing should be a mandatory requirement for blood donation [5], particularly as it can be a surrogate marker for high-risk behaviour associated with other non-tested infectious agents [2, 3].

Syphilis is surging globally, with substantial increases noted in several regions, including the United States, Europe, Japan, Australia and China [6]. Syphilis prevalence estimates are calculated for consensus positive infections (which include screen reactive, confirmed-positive infections based on total antibodies) and active infections (a subset of consensus positive that are also rapid plasma reagin [RPR] positive). Recently, the Transfusion Transmissible Infections Monitoring System Program in the United States reported a marked increase in syphilis prevalence in donations, which is considered to be a reflection of overall increasing trends in the general population (from 15.9/100,000 in 2012 to 51.5/100,000 in 2021) [3]. This resurgence is also seen in low- or middle-income countries (LMICs), with >6 million new cases occurring annually and causing foetal and neonatal morbidity and mortality [7].

The laboratory diagnosis of syphilis is complex and no single diagnostic assay is able to accurately determine both latent and active infections [8–12], although expectedly the higher cost treponemal antigen-based diagnostics assay outperform the lower cost non-treponemal assays [11]. Because many LMICs cannot afford the more expensive treponemal antigen-based assays for primary screening, they use an algorithm approach, and first screen with a low-cost non-treponemal assay (e.g., RPR) and then confirm reactive samples with the higher cost treponemal assay(s) [11, 12]. Many transfusion services also use a combination of data to determine who has an active or recent infection, including their previous donation testing results and the clinical history provided. In contrast, most high-income countries (and some LMICs where a low-cost treponemal assay is available) first use the more sensitive but more expensive treponemal-based assay for primary screening, followed by confirmation of reactive samples with either (or both) a different treponemal assay and/or non-treponemal assay (reverse-algorithm) [11, 12]. Despite this, not all treponemal antigen-based assays are equal, and a range of technological variations exist including enzyme immunoassays (EIAs), *T. pallidum* particle agglutination (TPPA) and its hemagglutination variation, the TPHA, and lateral flow point of care (POC) assays, each with their own limitations in sensitivity and specificity and affordability [8–12]. Thus, there remains a need, especially in LMICs, for low-cost, high-sensitivity, easy-to-use assays for the detection of treponemal antibodies that are used to diagnose syphilis, ideally those suitable for use with existing laboratory resources.

Recently, the Kode Technology platform [13] has been shown to be suitable for the detection of SARS-CoV-2 antibodies using existing blood transfusion services laboratory infrastructure [14–17]. With the peptide sequence of the syphilis treponemal spirochete *T. pallidum* well established [7, 8], using the same principles as for SARS-CoV2–kodecyte development, we investigated the opportunity to create *T. pallidum* lipoprotein (TmpA)–kodecytes for use on existing routine blood antibody screening column agglutination testing (CAT) diagnostic platforms.

MATERIALS AND METHODS

Reactive plasma samples ($n = 150$) were obtained from blood donors donated blood at Tata Medical Center, Kolkata—initially identified

with the Syphicheck modified TPPA device (Syphicheck-WB, Viola Diagnostic Systems, India) [18] and/or confirmed reactive with the EIA-OCD, (VITROS System Ortho Clinical Diagnostics, Pencoed, UK) and/or RPR (Carbogen, Coral Clinical System, India) assays. Non-reactive (NR) plasma samples ($n = 2072$) were from healthy blood donors and obtained from the Tata Medical Centre (Kolkata, India) and confirmed NR with the Syphicheck, RPR and EIA-OCD methods. Syphicheck-WB is a two-site double recombinant antigen (47 kDa and 17 kDa) sandwich immunoassay for the detection of total (IgM and IgG) antibodies to *T. pallidum* [18]. Although Syphicheck-WB is not a quantitative assay, it has been found to give positive results up to a dilution of 64 when qualitatively validated by testing different dilutions of plasma. The cut-off in EIA-OCD is 1.0 for reactivity. Ethical committee approval was waived by the institutional review board as donor details were not captured, only declassified blood samples were used and consent was obtained from each blood donor for the syphilis testing according to the national policy.

TmpA function-spacer-lipid constructs and kodecytes

The selection and design of synthetic peptide-based function-spacer-lipid (FSL) constructs is complex (see Appendix S1) [13–15]. In brief, the published syphilis peptide sequences for *T. pallidum* were used to find candidate non-glycosylated peptide epitopes suitable for construction as FSL constructs [13–15]. Following extensive serologic evaluations of these three candidates, TmpA1 were selected as the best candidate for field trials (see Appendix S1) [14]. Terminology for describing FSL constructs and the resultant kodecytes are as described in detail elsewhere [13–15, 19].

In brief, preparation of kodecytes [13] involved mixing a solution of FSL construct (e.g., 2.5 µmol/L) with washed packed group O red cells, incubation at 37°C for 2 h and storage in red cell stabilizer (ID-CellStab, DiaMed GmBH, Switzerland) solution at 4°C. No washing is required at any stage (and stored kodecytes were not washed prior to use). Kodecytes were rested overnight before use, and used within 21 days. A detailed protocol for the preparation of TmpA–kodecytes is available (see Appendix S1).

TmpA–kodecyte assays

TmpA serology was undertaken in routine CAT platforms with methodologies and scoring systems as recommended by the manufacturer, including the use of the grades 4+, 3+, 2+, 1+ and *w* to indicate weak positive reaction. Example CAT reactions are shown in Figure 1. Samples were tested in both the Bio-Rad ID-system with Coombs anti-IgG card (CAT-BIO; Bio-Rad Laboratories, DiaMed GmBH, Switzerland) and the Ortho BioVue system (CAT-OCD; anti-IgG cards; Ortho Clinical Diagnostics, Pencoed, UK). As part of the validation evaluations, unmodified group O cells (the same cell as used to make the kodecyte) were also used as controls, in addition to known positive and negative controls.

RESULTS

TmpA–kodecyte agreement rate (NR samples)

Against 2072 Syphicheck-defined NR blood donor samples, 24 (1.16%) were reactive with TmpA–kodecytes (Table 1). Of these reactive NR samples, most had reactivity grades 2+ or greater, and all were unreactive with unmodified cells, indicating the reaction was due to IgG/IgM directed against the TmpA1 peptide on the kodecyte.

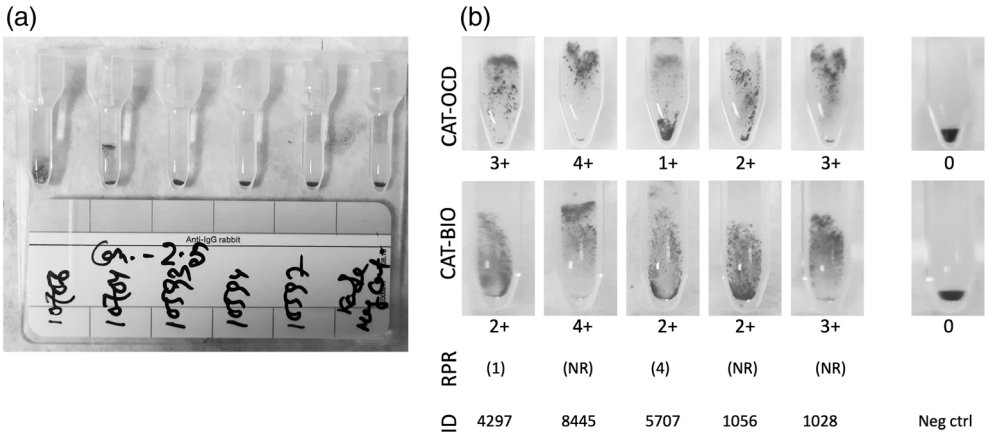

FIGURE 1 (a) Selected example of column agglutination testing (CAT)-BIO reactions of *Treponema pallidum* lipoprotein (TmpA)–kodecytes against Syphicheck (and enzyme immunoassay [EIA]-OCD) non-reactive (NR) donor samples. The false-positive reactions seen in lanes 1 and 2 were observed with 1.16% of NR samples. Lanes 3–5 show typical negative reactions against TmpA–kodecytes, whereas the negative reaction in lane 6 is against with unmodified cells (the same cell as used to make the kodecytes). (b) Selected examples comparing CAT-OCD versus CAT-BIO reactions with TmpA–kodecytes against Syphicheck (and EIA-OCD)-reactive donor samples. The serologic score is indicated as is the reciprocal of the rapid plasmin reagin (RPR) titre which is shown in brackets; this figure has been created by assembling individual images from different gel cards, scaling them to similar size and conversion to black and white.

TABLE 1 TmpA–kodecyte results for 2072 non-reactive (NR) donor samples.

NR samples (Syphicheck, RPR and EIA-OCD)				
			TmpA–kodecyte serologic grade	
Result	*n*	%	CAT-BIO	CAT-OCD
NR	2048	98.84%	0	0
Reactive	3		1+	1+
Reactive	1		2+	1+
Reactive	19		2+	2+
Reactive	1		4+	4+
Reactive (total)	24	1.16%	+	+

Abbreviations: CAT, column agglutination testing; EIA, enzyme immunoassays; RPR, rapid plasmin reagin; TmpA, *Treponema pallidum* lipoprotein.

TABLE 2 Correlation between CAT-BIO and CAT-OCD serologic grades against 150 Syphicheck-reactive donor samples.

Platform serologic grades against TmpA–kodecytes						
	CAT-BIO (grades)					
CAT-OCD (grades)	4+	3+	2+	1+	*w*	0
4+	10	(1)		(1)		
3+		47	(3)			
2+			63	(1)		
1+				19	(1)	
w						
0						4[a]

Note: Non-identical grades are indicated in brackets.
Abbreviations: CAT, column agglutination testing; TmpA, *Treponema pallidum* lipoprotein.
[a]2/4 were 1+ reactive with 5.0 μM TMPA1–kodecytes.

TmpA–kodecyte agreement rate (reactive samples)

Of 150 samples that were identified as reactive with the Syphicheck diagnostic as well as with EIA-OCD, 146 (98.8%) tested reactive against TmpA–kodecytes (Table 2). Of the four samples testing reactive with Syphicheck but NR with TmpA–kodecytes, all were NR by RPR (see Appendix S1) and one was borderline reactive by EIA-OCD. Overall, the correlation in grades between the CAT-BIO and CAT-OCD platforms was excellent with 149/150 (99.3%) of grades being within 1 grade of consensus (Table 2). Of the 7/150 samples (4.7%) that were outside of identical grades, all except one were only one grade lower in grade in the CAT-BIO platform. The one outlier (with identical results in repeat testing) had a 4+ grade in the CAT-OCD platform and 1+ grade in the CAT-BIO platform (Table 2). The reason for this large variation in reaction grade between platforms could not be explained.

The reactive rate for the RPR assay against these same samples was 58.0% (87/150 samples were reactive, see Appendix S1). The correlation of the TmpA–kodecyte grades with RPR titre was generally poor (see Appendix S1).

DISCUSSION

In blood centres, the mandatory screening for syphilis antibodies is done using immuno-serology-based methods [8–12]. The cost of the diagnostic assay is a significant factor in the decision of what platform is used, especially for LMICs.

There are essentially two categories of syphilis serological diagnostic methods (for the detection of syphilis antibodies). The first is the non-treponemal methods which use a cardiolipin, lecithin and cholesterol complex to detect anti-lipoidal antibodies (a consequence of syphilis infection); these assays include the venereal disease research laboratory (VDRL) and RPR tests [1], which have sensitivity in the range of 61%–78% for detecting latent syphilis and 78%–86% for detecting early syphilis infection [20]. However, a serological diagnosis of syphilis cannot be made using a single assay such as RPR. It must be confirmed with the use of either the traditional or reverse sequence algorithm. The second category of serologic assay, of which there are four main variations, uses treponemal antigens (natural or recombinant) to detect treponeme-specific antibodies with sensitivity in the range of 82%–100% across the spectrum of the disease [1, 8, 12, 18] and includes a variety of direct and indirect immunoassays [8–12]. The primary basis of these methods is to use *T. pallidum* antigen and labelled secondary antibodies to generate a quantitative result with sensitivity and specificity of >95% (reviewed in detail elsewhere) [8]. The third serological method variant is the *T. pallidum* particle agglutination (TPPA) assay. In this assay, *T. pallidum* antigen is coated onto coloured gelatine particles which in the presence of serum containing specific antibody will aggregate, which is interpreted as reactive. The TPPA test has a relatively high specificity rate of >97%, although it has a lower sensitivity rate for primary and latent syphilis (>86%) [9, 10]. The fourth serologic TPPA-like method, commonly used in LMICs due to their low cost, are the rapid POC diagnostic tests which use treponemal-specific antigens either in strips and/or on carrier particles [18, 21]. Although the sensitivity and specificity of these POC assays are reported to be very high in clinical laboratories [18, 21], there is some evidence that they do not perform as well (with sensitivity and specificity as low as 50%) in less regulated clinic settings [22].

In contrast to the above described treponemal antigen serologic assays, the TmpA–kodecyte assay does not use natural or recombinant antigens, but instead uses a comparatively small synthetic 15 amino acid peptide. This alternative approach is achieved by first identifying potential non-glycosylated epitopes of *T. pallidum* using a range of predictive algorithms and online tools [14, 15], followed by refinement to be compatible with FSL conjugation chemistry, and then optimization using serology for sensitivity and specificity (see Appendix S1). From the initial >20 potential candidates predicted, three were made into FSL constructs and after extensive serological testing FSL-TmpA1 including against reference standards and clinical samples was selected as the best [14]. In the developmental phase of this project [14], against 211 clinical syphilis samples (EIA-confirmed reactive), it was found that TmpA-10–kodecytes (10 μmol/L) had 98.6% agreement rate, in contrast to TPPA which had 89% and RPR which had 61% [14]. External WHO/CDC syphilis quality control samples (100% agreement rate) further validated the sensitivity of the TmpA–kodecytes, as did the NR results with 157 samples reactive for non-syphilis pathogens and autoantibodies [14].

The detection of treponemal antibodies may indicate a recent, past or successfully treated infection. An initial syphilis seroreactive donor is considered to have an active infection if they further test positive on a RPR test. A positive result for reagin indicates a recent infection at 3–6 weeks after a risk exposure. In this study, the Syphicheck assay was chosen as the diagnostic assay for comparison as it is the dominant TPPA assay used in India, with validated sensitivity and specificity [21]. The novel TmpA–kodecytes-based assay might be used as an alternative to the Syphicheck assay and has the potential to become the primary screening assay in a reverse sequence algorithm. Subsequently, the status of an active infection can be confirmed by the RPR test. In this study, reactive samples were primarily selected to be reactive by the Syphicheck assay, a process which creates a sensitivity selection bias [9]. As the Syphicheck assay is reported to have a sensitivity of 95.3% [21], theoretically 4.7% of true-positive samples will be NR with the Syphicheck assay, but as they were not selected for analysis, their reactivity against TmpA–kodecytes is unknown. With respect to the agreement rate of the 150 donor samples identified as reactive with the Syphicheck diagnostic, 97.3% were also tested reactive with TmpA–kodecytes, in contrast to 58.0% by RPR.

The agreement rate of the TmpA–kodecyte assay against 2072 NR donor samples was 98.84%, meaning that there was a reactive (false-positive) rate of 1.16% compared with the Syphicheck false-positive rate which ranges from 0.16% to 0.34% (see Appendix S1). Although the TmpA–kodecyte false-positive rate was higher than optimal, the rate of 1.2% was considered acceptable for the TmpA–kodecyte assay to be used for primary screening together with confirmation using another treponemal antigen diagnostic (e.g., TPPA/EIA). Even when including the cost of the CAT platforms, compared with other assays [10], the TmpA–kodecyte assay is a low-cost assay (e.g., 0.5 mg of FSL-TmpA1 at a cost of USD 1000 will enable more than 100,000 CAT assays as 2.5 μmol/L kodecytes) [15, 22] and is compatible with high-throughput screening. Therefore, the development of this new TmpA–kodecyte assay may be useful for blood centres in LMICs that are already using CAT platforms for pre-transfusion testing.

Approximately, 90% of the new syphilis cases reported every year occur in developing countries where there is often a lack of resources necessary to purchase and perform treponemal-based tests [23]. In addition to utilization for routine blood donor screening having access to a low-cost treponemal-based assay, particularly one which utilizes existing laboratory infrastructure may have an impact of syphilis diagnosis in these regions. Sample testing of blood donors offers a unique opportunity to screen healthy individuals for the presence of antibodies to infections on a population level [24]. This is a role that blood establishments can play in informing public health policy [22], and this type of serosurveillance could be expanded in the future for emerging infections [24]. Additionally, although blood services typically do not undertake screening for syphilis antibodies in samples other than their donor cohort, with the availability of a low-cost, high-throughput treponemal diagnostic like the TmpA–kodecyte assay, there is a possibility they could provide this service.

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CONFLICT OF INTEREST STATEMENT

Stephen M. Henry and Nicolai V. Bovin are employees and stockholders in Kode Biotech, the patent owner of Kode biosurface engineering technology. All other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings are available from the corresponding authors upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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