TECHNICAL REPORT

Novel approaches to testing for sexually transmitted infections, including HIV and hepatitis B and C in Europe

ECDC TECHNICAL REPORT

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Abbreviations

CSW	Commercial sex workers
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EU	European Union
FDA	Food and Drug Administration
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IDU	Injecting Drug User
IVD	In-Vitro Diagnostic
MSM	Men who have sex with men
MHRA	Medicines and Healthcare products Regulatory Agency
NAATs	Nucleic Acid Amplification Technologies
POC	Point of Care
STI	Sexually Transmitted Infection
WHO	World Health Organization
UK	United Kingdom
USA	United States of America

Executive summary

Testing strategies are central to the control of sexually transmitted infections (STIs), human immunodeficiency virus (HIV) and hepatitis B and C. Accurate testing enables treatment of those infected and subsequent reduction in infectiousness, reduced clinical consequences, identification as well as treatment of potentially infected partners and opportunities for health promotion and behaviour modification due to awareness of infection. Nonetheless, there is huge variation in the availability of current routine diagnostic tests within Europe. Recent changes in the field of testing for STIs, HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) include the widespread implementation of nucleic acid amplification technologies (NAATs) for chlamydia and gonorrhoea diagnosis and the development of HIV screening tests that are easy to use and give a result almost immediately. Such technological advances can open up opportunities for more accurate, near-patient testing, provision of rapid results, or non-invasive sampling. Developments in communication technology in recent years have enabled the emergence of e-health (electronic-health) and m-health (mobile-health) activities.

A framework was developed to structure and categorise the advances and novel approaches, consisting of i) test technical principle and biological sample, ii) person-context, and iii) information cascade, together with the cross-cutting themes of evaluation, regulation and quality control and quality assurance. A literature search was conducted using broad search criteria for recent publications from European countries, the United States, Canada and Australia. Further information and examples were obtained from grey literature and online searches and input from experts.

Amplification, molecular techniques and non-amplification techniques such as lateral flow have been applied to test for a wide range of infections. Nucleic Acid Amplification Technologies (NAATs) tests offer accurate diagnosis, while lateral flow and flow-through tests require limited equipment, ease of use and can give results almost immediately. Rapidity together with the accuracy of molecular diagnostics has been made possible with the advent of microfluidic and nano-based NAATs technologies. Tests for chlamydia and gonorrhoea, and HIV viral load are in development. Microfluidic and nano-based technologies use very low reagent volumes which improve efficiency, reduce costs and increase portability. Non-amplification point of care (POC) tests for HIV based on lateral flow and flow-through principles have been extensively evaluated and implemented in service provision. They enable screening results to be given to participants within 30 minutes and hence delivered at the same visit. However, development of POC devices and particularly any future self-testing devices will be challenged by the need for simple methods to collect the biological sample and apply it to the device, with minimal sample processing by the user to minimise operator error.

Expanding testing for STIs, HIV, HBV and HCV to healthcare settings outside specialist health care services and community services can be used to expand access to testing and to target key populations. HIV and chlamydia testing are leading the way in moving testing to these types of venue. A systematic review reported that HIV testing in community settings can be successful in diagnosing previously undiagnosed HIV infections in many most at-risk populations, and is acceptable to both the target group and staff undertaking the tests.

The use of the internet for recruiting young people or other target groups to test for STIs is considered to be the most innovative method of offering home-testing, offering convenience and privacy through postal receipt of kits while not limiting the target population by geographical location or the necessity of being registered with a healthcare organisation, school or other list. It is now common practice in many settings to disseminate results by SMS message, considerably reducing staff time for giving out results and managing clinic workload. An effective component of STI control strategies is partner notification and treatment: and there are a number of examples of internet tools which have been developed with the aim of helping both provider-led and patient-led partner notification.

Evaluations of new diagnostics and new approaches to testing are required to ensure effective and cost-effective use and implementation of novel technologies and approaches. Diagnostic devices are regulated at the EU-level under the Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic (IVD) medical devices, and the Commission Decision of 3 February 2009 amending Decision 2002/364/EC on common technical specifications for IVD medical devices. Although there are minimum performance standards for devices to detect HIV, HBV and HCV, these do not exist for other infections. Self-testing and POC IVD devices also fall under the scope of the European Directive and are additionally required to perform appropriately, given the skills and means available to the intended users, and the variation that can reasonably be anticipated in their technique and environment. The regulation of health-related mobile phone apps and websites is currently being debated in both Europe and the US. There is country specific legislation regulating the availability of POC diagnostic devices directly to the public. Quality control of the production of commercially available diagnostic tests is regulated by CE-marking. Quality assurance and quality control of testing facilities however are not regulated at the European level. European countries may have their own accreditation scheme.

New testing technologies combined with modern information and communication systems will enable the development of novel testing pathways. These novel approaches have the potential to improve access to, and hence uptake of, testing among individuals and population groups at risk as well as increase the proportion of infected individuals treated earlier in infection. These novel approaches will have clinical impact by improving the prognosis for those with infections as well as public health impact by reducing onward transmission and thus incidence and prevalence of infection.

Research priorities for novel technologies for HIV, HBV, HCV and STI testing include: developing models, or frameworks, for strategic, evidence based decision making on adoption of novel approaches to testing; technology adoption type reviews of novel technologies and approaches; operational research on the implementation of testing programmes; and continued development and improvement of the technical aspects of testing devices.

1. Introduction

This report focuses on novel approaches to testing for sexually transmitted infections (STIs), human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) that are relevant for the prevention and control of these infections at EU/EEA level. 'Novel approaches' captures both technical advances in STI, HIV, HBV and HCV tests as well as new opportunities for initiating and conducting testing and managing results, treatment and surveillance that the changes in technology facilitate. The report is not intended to comprehensively review all the novel testing devices currently available or in development, but rather to provide an overview of recent advances and to identify the opportunities and challenges these present with regard to the diagnosis of infections and more broadly public health.

Epidemiological situation

Rates of reporting of STI, HIV and hepatitis vary widely across Europe, with differences in the epidemiology of infections but also in national testing policies, practices and surveillance systems [6] [7]. Overall, STIs are considered to be under-reported, with reporting rates reflecting both the number of tests performed and the accuracy of the tests themselves, particularly for asymptomatic infections. Key populations at risk include young people, men who have sex with men (MSM), commercial sex workers (CSW), migrants and injecting drug users (IDU).

Chlamydia trachomatis is the most frequently reported STI in Europe, with 345 421 cases in 24 EU/EEA Member States in 2010 [7].The number of reported chlamydia infections has been rising, at least in part due to increased testing and the use of more sensitive diagnostic tests. Nonetheless, the true incidence in young people aged 15–24 years (the age group most affected) is likely to be much higher than the reported rate of 0.8% as this infection is often asymptomatic. In the UK, for example, rates of positivity among asymptomatic young people screened for chlamydia have been found to be around 8% [8]. In 2010, 32 098 confirmed cases of gonorrhoea were reported by 28 EU/EEA countries. There was a slight reduction reported in several countries between 2006 and 2010 but no consistent pattern across the region. One third of all gonorrhoea cases were reported in people aged 25–34 years and one quarter of the cases affected MSM [7]. Antimicrobial resistance in *Neisseria gonorrhoeae* is of increasing concern, with the occurrence of untreatable gonorrhoea cases becoming a real possibility.

The rate of new diagnoses of HIV reported in EU/EEA has been fairly stable since 2004, with 27 116 newly diagnosed cases reported in 2010 [9]. However, it has been estimated that 30% of individuals infected with HIV in Europe are undiagnosed [10]. Furthermore, many people with HIV remain undiagnosed until late in the course of infection and so cannot benefit from earlier treatment that reduces morbidity and mortality and lowers the risk of transmission. Recent studies have shown the concept of treatment as prevention in discordant couples to be effective [11]. Early diagnosis is a key factor for reducing onward transmission.

In 2010, 14 745 confirmed cases of HBV infection were reported by 27 EU/EEA Member States. Between 2006 and 2010, a slight reduction was seen in acute cases while increasing rates were reported for chronic infections (ECDC's forthcoming report Hepatitis B and C infections in Europe, 2006–2010). A sero-epidemiogical study found wide variation in HBV infection and vaccination markers [12]. Hepatitis B vaccination is universally offered as part of childhood immunisations, in addition to at-risk groups, in 20 EU/EAA countries. The other countries operate selective vaccination policies for high-risk groups only [13]. Testing for HBV enables access to treatment or vaccination depending on the test result. HCV infection is the most common type of viral hepatitis reported in 26 EU/EEA countries, with 26 678 confirmed cases reported in 2010 (ECDC's forthcoming report Hepatitis B and C in Europe, 2006–2010). Prevalence estimates in the general population vary between 1 and 5% across Europe [14]. HCV incidence data suggest an increasing trend over time [15]. Under-reporting, lack of representative, population-based data and differences in case-definitions lead to considerable uncertainty in these estimates and interpreting comparisons between countries or trends [14, 15]. Recent advances in treatment for HCV infection have been a major driver for increasing rates of diagnosis.

Role and provision of testing

Accurate testing for STIs, HIV, HBV and HCV enables treatment of those infected and subsequent reduction in infectiousness, reduced clinical consequences, identification as well as treatment of potentially infected partners, and opportunities for health promotion and behaviour modification due to awareness of infection. Testing strategies are thus central to the control of these infections, as well as Wilson and Jungner's classic principles of screening applicable [16]. Effective testing requires access to a system in which there is high uptake and accuracy of diagnostic tests, appropriately rapid communication of results, and correct management and treatment of positive cases and their partners.

Many countries have implemented public health programmes to increase testing in both at-risk populations and others, such as pregnant women (antenatal HBV, HIV and syphilis screening). A number of countries have established chlamydia screening programmes which have increased the number of diagnoses. ECDC guidance on 'Chlamydia control in Europe[1]' recommends that control activities, in addition to being evidence-based and taking into account the local infrastructure and resources, are built in a step-wise manner that ensures primary prevention and case management are in place before consideration of more complex interventions such as screening [17]. Furthermore, in order to control the chlamydia-associated disease burden in Europe, any comprehensive control programmes should be targeted to reach those populations most at risk, such as young people [18].

Reported rates of HIV testing among groups most at risk vary widely, from less than 1% up to 84% for injecting drug users and less than 1% up to 70% for MSM. ECDC guidance on increasing the uptake of HIV testing in Europe recommends developing testing in a range of non-traditional sites and using the most setting-appropriate testing technologies, including rapid (POC) tests, in order to overcome barriers to testing among those at higher risk [19].

The role of testing for HPV differs slightly from other STI tests. HPV infection can cause changes to the cells of the cervix that can lead to cervical cancer if left undetected and untreated. HPV is considered a necessary but not sufficient cause of cervical cancer. HPV infection is however extremely common in sexually active population with the vast majority of infections resolving spontaneously. The difficulty with HPV testing is therefore to distinguish clinically relevant infections i.e. those that might lead to cervical cancer, from transient or low-risk infections.

There remains a huge variability between resource-rich and resource-poor countries within Europe regarding the availability of current routine diagnostic tests, with many Eastern European countries still relying heavily upon use of syndromic management for most STI cases [20, 21].

Advances in testing technologies

In the last few years there have been significant changes in the field of testing for STIs, HIV, HBV and HCV. Nucleic acid amplification technologies (NAATs) in chlamydia diagnostics, for example, which until very recently required sophisticated laboratory facilities and technical skills are now in widespread use across much of Europe [22], with 16 out of 25 reporting EU/EEA countries using NAATs for more than 50% of chlamydia testing [23]. NAATs offer the opportunity for chlamydia and gonorrhoea testing in new settings and for dual testing for both infections. These tests, performed in laboratories using highly automated machines, have high sensitivity and specificity, fast turnaround times for results and enable the use of non-invasive specimens.

Ideally new diagnostics will meet the ASSURED criteria of the World Health Organization: affordable; sensitive; specific; user-friendly; robust and rapid; equipment-free; deliverable to those who need them, especially for less well resourced populations [24].

There have been improvements in both accuracy and the ability to test earlier post-exposure for HIV using fast turnaround antibody-antigen detection-based tests. Rapid, easy to use, accurate HIV screening tests are also now available, some of which can give a result almost immediately [25]. Similarly to HIV, avidity testing has been applied to HBV and HCV diagnosis to distinguish between acute and chronic hepatitis infections [26, 27]. A number of companies have developed multiplex rapid tests for HIV, HBV, HCV and syphilis; however, the performance characteristics of these tests require independent validation in laboratory and field settings.

The development of micro and nano-electromechanical systems since the late 1980s has allowed complex mechanical and electronic components to be fabricated at the micro-scale within a single device. This lab-on-a-chip technology has developed in the past decade with bench-top laboratory processes being scaled down into single microfluidic chips.

Such new technologies can open up opportunities for more accurate, near-patient testing, provision of rapid results, or non-invasive sampling. Biological sample collection (e.g. for laboratory-based chlamydia testing) and testing (e.g. for HIV using rapid POC tests) are now frequently conducted outside traditional clinical settings. Innovative approaches to testing for HBV and HCV, such as community-based testing in the UK for minority ethnic population groups at higher risk, have also been piloted with success [28, 29].

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[1] Available at: http://ecdc.europa.eu/en/publications/Publications/0906_GUI_Chlamydia_Control_in_Europe.pdf

These advances offer potential advantages but also raise new challenges. Testing in lower-risk groups, where prevalence is lower, or for infections which are less prevalent, will impact on the positive predictive value of tests and necessitate the use of a confirmatory test (or tests with built-in confirmatory targets) [30]. NAATs do not currently provide information on antibiotic sensitivities; a problem of particular relevance for gonorrhoea where the risk of receiving ineffective treatment increases without such information can further promote the spread of antimicrobial resistance. Furthermore, there is the potential that organisms can evolve to evade detection when NAATs are used widely, as occurred with the Swedish variant *C. trachomatis* strain which had a 377bp deletion in the plasmid region targeted by some chlamydia NAATs. This led to false-negative results and the recent identification of *N. gonorrhoeae* isolates that lack the *porA* pseudogene target identified by some PCR assays, again leading to false negative results [31–33].

Advances in communication technologies

In recent years, there have been phenomenal developments in communication technology and the emergence of e-health (electronic-health) and m-health (mobile-health) as new fields. Communication technologies enable access to information, biological sample collection and testing outside of healthcare settings, and facilitate communication of results. Access to communication technologies is extremely high in Europe where, in 2008, 87% of the population aged 15–74 years used a mobile phone and even in those countries with the lowest usage (Portugal and Romania), more than 77% used a mobile phone. Furthermore, 58% of the population used the internet, with this figure rising to 88% of 16 to 24 year olds [34].

Communication technologies have been exploited for many health and healthcare related purposes. This includes the basic provision of health promotion information on websites and internet-based continuing medical education for clinicians. SMS messages are used to remind patients of healthcare appointments and in some circumstances to send results to patients. Mobile-phone and digital pen technology has been used to facilitate midwifery care, [35] and apps-technology used to link with self-testing devices for the management of chronic diseases such as diabetes [36]. A number of companies have developed readers to provide a more objective and standardised interpretation of rapid or POC tests [37]. These readers can transmit data to a central database making it easier to link case detection to surveillance, especially from more remote areas. The readers can also transmit a photo of the test results for quality monitoring.

2. Methods

A framework was developed (Table 1) to describe novel approaches to testing. The framework has been used to structure and categorise the advances and novel approaches under the three testing pathway components: i) test technical principle and biological sample, ii) person-context, and iii) information cascade. Sub-components within the main pathway components were defined (as detailed in Table 1) together with the cross-cutting themes of evaluation, regulation and quality control and quality assurance.

Table 1. **Framework for categorising novel approaches to testing for STIs, HIV, HBV and HCV.**

Pathway component	Test technical principle and biological sample	Person-context	Information cascade
Scope	The test principle and biological sample type used to detect infection	Testing criteria and operational issues around sampling, testing and treatment access	Methods of communication with target and testing populations
Sub-components	1. Test technical principle; test requirements, performance and characteristics 2. Biological sample types and sampling methods (e.g. use of non-invasive samples and self-collected samples) 3. Time to test result (e.g. point of care testing)	1. Access to sampling/testing in non-specialist health settings 2. Biological sample collection outside healthcare settings i.e. 'community' venues 3. Access to testing via the internet 4. Self-testing 5. Novel clinical pathways	1. Use of new communication technologies to increase testing/retesting rates 2. Use of new technologies for risk assessment to target testing 3. Disseminating test results and ensuring entry to treatment pathway 4. Partner notification 5. Surveillance
	Evaluation		
	Regulation		
	Quality assurance and quality control		

A literature search was conducted using the search strategy shown in Appendix 1. The search criteria used were necessarily broad as it was not possible to clearly identify 'novel' or 'new' approaches from specific terminology or MeSH headings. The search was limited to publications from 1st January 2009 and to articles from European countries, the United States, Canada and Australia. Grey literature and online sources were searched using an internet search engine and the search terms shown in Appendix 1.

A large number of publications were through our (necessarily broad) searches (Appendix 1). One of two researchers reviewed titles (n=3,493), followed by abstracts (n=459) of potentially relevant articles, and finally full articles. Data were extracted from studies and reports considered to be presenting a novel angle to testing and systematically collated. Studies and reports were categorised by the pathway component against which they most impacted (Table 1). The information was further supplemented by additional web and literature searches, consultation with experts in the field and references cited in selected articles.

3. Results

Test technical principle and biological sample

Testing methodologies

Expansion of existing technology

New infectious disease testing methods are continually being developed. Many of these are based on existing technologies that are being produced by a new manufacturer, being enhanced or being applied to a new diagnostic target. Some examples of extensions of existing NAATs are as follows.

- Performance characteristics of chlamydia and gonorrhoea NAATs from new manufacturers have recently been reported [38].
- NAATs have been developed to detect *T. pallidum*, where the mainstay of diagnosing syphilis is treponemal-specific and nontreponemal serology assays, and dark-field microscopy at the POC in the presence of early syphilitic lesions [39]. Such NAATs for early syphilis offer the potential for fast turnaround times, relatively simple performance and direct detection of pathogen, [40] but performance characteristics have been variable [40, 41]. Real-time PCR might be a useful tool in the diagnosis of syphilis by identifying treponemes, for example from ulcer swabs or lymph node aspirates. There are currently no FDA-approved syphilis NAATs. One commercially available test was identified that states it will be CE-marked but no performance data could be found [42].
- NAATs for HIV have been developed. These are mainly used to measure viral load and are not recommended as a screening test in developed countries, where prevalence is low, due to cost and the possibility of false-positive results, [43] but they may be useful in detecting very early infection. NAATS for HIV, HBV and HCV detection for use in blood donation screening have also been developed and integrated into donor screening in some countries. [44–46]
- NAATs and non-amplification based commercial assays have been developed for the detection of human papillomavirus (HPV).
- NAATs are replacing culture as the gold-standard for the direct detection of herpes simplex virus (HSV) 1 and 2 [20, 47].

The first FDA-approved rapid HCV test has been developed based on the same lateral flow immunoassay principles as the company's HIV antibody test [48]. Lateral flow-based assays have also been developed as rapid tests for detection of *Trichomonas vaginalis* [49] and chlamydia with varying success [50, 51].

New technologies

Rapidity together with the accuracy of molecular diagnostics has been made possible with the advent of microfluidic and nano-based technologies. These micro-engineered platforms allow robust and reproducible reactions to occur at very low reagent volumes which improve efficiency and speed of reactions. Further advantages of the miniaturisation of laboratory protocols include cost reduction, portability, disposability and better process control. These technologies have thereby enabled the development of NAATs, which could be used at the POC, and have been successfully employed for testing of other (non-STI) infectious diseases.

Several companies have developed microfluidic or nano technology NAATs tests designed around systems of infection-specific disposable cartridges that run using the same base unit [52, 53]. Each cartridge contains a series of chambers in which the NAATs processes are conducted, including sample preparation and DNA extraction, amplification and detection. Such systems have thus far gained FDA approval for cartridges to diagnose healthcare acquired infections, including meticillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*, *Mycobacterium tuberculosis* with rpoB gene for rifampicin resistance and influenza amongst others. STI cartridges which test for chlamydia and gonorrhoea are under development, as are HIV viral load tests [54]. The simplicity of these technologies for the user, the availability of small foot-print base units and the short turnaround time may open up opportunities for conducting NAATs-based testing outside central laboratory facilities. Remote systems for quality control of such instruments, which is important for decentralisation of testing, are also being developed.

Although in its infancy, paper-based microfluidic analytical devices are currently being investigated for various applications [55]. Such devices incorporate the merits of microfluidics and the established technology of lateral flow assays performed on porous media. They are produced by patterning paper with hydrophobic material to create hydrophobic barriers and hydrophilic channels. Initially considered a low-cost diagnostic solution for developing countries, the expansion of different patterning methods and manufacturing processes, has seen this technology becoming an important candidate in POC testing devices [56].

Point of care patient testing

POC testing in itself is not new, with gram-stains and dark field microscopy coming under this umbrella [57]. Currently commercially available POC, self-contained tests for STIs, HIV, HBV and HCV are based on solid-phase, lateral flow, flow-through and agglutination methods [1]. Ideally POC tests should be sensitive and specific, however there may be situations where a less sensitive POC test might result in more infected individuals being treated than a more accurate but slower turnaround test because of failure of infected persons to return for treatment [58]. Where the failure-to-return rates are low, this benefit may not be seen, although a POC test will enable faster treatment and potentially reduce onward transmission. Rapid diagnostics and use of modern communication technologies are particularly important where patients cannot or do not return to clinics to obtain test results [59].

Point of care HIV tests have been extensively evaluated and implemented in service provision. They enable screening results to be given to participants within 30 minutes, and hence delivered at the same visit [19]. Some tests are very rapid with turnaround times of 1–2 minutes. The use of these tests has been shown to be highly acceptable to users in STI clinics and other healthcare settings and community venues. They have also been shown to increase the proportion of testers who receive their result and who receive their results on the same visit [60]. The problem of testing negative during the window-period between infection and the production of antibodies with antibody-detection based tests is an issue, and fourth generation HIV tests (both laboratory and POC) have attempted to go some way to overcome this through the inclusion of a target for p24 antigen [61]. There remains however some question as to the benefit to be gained by using fourth generation POC tests for rapid screening over third generation, particularly in low-risk populations where the positive predictive value of such tests may be prohibitively poor [62] [63]. Point of care combined HIV and syphilis tests are currently in development [64].

Rapid HCV tests have also been developed to be simple to use without the need for laboratory facilities, opening up the possibility of testing away from central laboratory facilities, for example in a mobile van, and targeting of at-risk populations. One US field study found targeting high-risk individuals through community -based organisations using rapid (result in 20 minutes) POC testing for HCV to be an approach acceptable to staff [65].

Several chlamydia rapid tests that can be used at the POC, based on non-amplified antigen detection, have been developed. Many however show poor performance characteristics with low sensitivity and specificity in independent evaluations [50] [51]. A systematic review of chlamydia POC tests (none of which were based on NAATs technology), concluded that from the limited data available laboratory-based NAATs are the most accurate and cost-effective method for diagnosing chlamydia [66]. As discussed above [52, 53] rapid NAATs-based tests for chlamydia that can be used at the POC are on the brink of becoming available [67]. These tests do however require some additional equipment, either the proprietary base unit or simple laboratory equipment.

For other STIs, non-amplification serologic assays for HSV 1 and HSV2 antibodies, based on lateral flow technology have been developed [47]. Rapid (result within ten minutes) POC tests for *Trichomonas vaginalis* are also available, based on immunochromatic capillary flow (dipstick). One study has shown such a test to have a sensitivity and specificity of 83% and 99% respectively when compared to a composite reference of culture and wet-mount [49]. Novel POC devices (based on lateral flow and flow-through technologies) for the rapid, simultaneous detection of non-treponemal and treponemal antibodies have also been developed, to act as both the screening and confirmatory test for diagnosis of syphilis [68] [69]. Automated readers that might reduce subjectivity in the interpretation of the output from such tests have also been developed [68].

Biological sample types and sampling methods

Advances in testing technologies are facilitating changes in biological sample-types, including the use of less invasive, smaller volume, easily transportable samples and sampling kits, without any decrease in performance characteristics, and potentially enabling improved detection from extra-genital sites. However, development of POC devices and particularly any future self-testing devices will be challenged by the need for simple methods to collect the biological sample and apply it to the device with no, or only very simple and acceptable sample processing by the user to minimise operator error.

Providing flexibility in the biological sample type required (either within the same platform or through different platforms) might increase the acceptability of a test and/or its ease of use in different population groups or venues. Many lateral flow tests for HIV and HCV are compatible with a range of sample-types including oral fluid, finger-prick, venepuncture and plasma and thus facilitate testing in community as well as healthcare settings [48]. A systematic review comparing oral and blood-based detection of HIV antibodies shows that although the pooled sensitivity and specificity of testing using the two specimen types are comparable, the lower positive predictive value of an oral test in a low prevalence setting is of concern [70]. Currently available NAATs for detection of chlamydia can handle and have been evaluated for urine, vaginal (self- or clinician collected), endocervical swabs and, although not licensed, for rectal and pharyngeal samples [71]. For some tests, differences in performance characteristics given different sample types have been found, with self-collected vaginal swabs being more sensitive than urine for testing in women [72]. Recent data suggest that the high sensitivity of NAAT tests enables detection of chlamydia in urine samples collected after only a short time has passed (20 minutes) since previous micturition [73]. NAATs tests for HSV enable improved direct detection of the virus from ulcers that have developed beyond the vesicular or pustular stages, compared to viral culture [47].

Dried blood and dried plasma spots have been well validated and are commonly used for HIV testing and monitoring [74]. Recently, the use of dried blood spots for detection of anti-HCV, detecting and quantifying HCV RNA and genotyping HCV has been reported [75]. This may further aid HCV testing in settings or populations where venepuncture is undesirable or samples need to be transported to central facilities, and potentially enable multiplex testing together with HIV [76]. Dried blood spots are currently used in the UK to test for hepatitis B surface antigen (HBsAg) in children born to HBV infected mothers: children are vaccinated at birth and re-tested using a dried-blood spot 12 months later to determine whether vaccination has prevented vertical transmission.

Molecular tests are not fastidious as to the viability of organisms and require only that the nucleic acid has not been denatured between collection and testing. Transportation of dry self-taken vaginal swabs sent by post (from participants requesting kits from www.iwantthekit.org in the US) has been shown not to considerably impact on the performance characteristics of NAATs compared to manufacturers' reported characteristics for chlamydia testing [77].

Whilst NAATs are sensitive and specific for gonococcal detection in the genital tract, the use of NAATs for detection of gonococcal from extra-genital sites (pharyngeal and rectal) is not considered sufficient alone, due to lack of specificity, with most guidelines recommending confirmatory testing using a NAATs with a different target sequence [78]. Commercially available NAATs are not licensed for samples from extra-genital sites [78]. Careful selection of the NAATs test and restriction of testing to populations with high prevalence of gonorrhoea has been recommended to maintain acceptable specificity when testing such sites, [79] and in such use NAATs have been shown to have high sensitivity (91–100% when compared to composite reference of two of the other three tests) and specificity (>98%) [80]. The selection of those extra-genital sites (ano-rectal and oral-pharyngeal) to be sampled is frequently based on sexual history: an approach which offers greater specificity than sampling based on symptoms alone [81]. Self-collected rectal swabs have been shown to be a valid specimen type for MSM and are feasible to collect both from clinic and community-based populations [82, 83].

The use of HPV testing to detect carcinogenic genotypes to screen women for changes to the cells of the cervix which might progress to cervical cancer, has the potential to enable the use of less invasive (e.g. urine or vaginal swabs) for first-line screening, rather than invasive clinician-collected cervical samples. Self-sampling and HPV testing may facilitate screening in some groups of persistent non-attenders [84, 85]. Large, population-based studies of HPV-based testing using cervical samples, suggest that screening programmes using HPV testing as first-line screen, with cytology to triage women with carcinogenic HPV genotype infections, would enable longer intervals between tests for women who are carcinogenic HPV genotype negative [86] [87].

Microfluidic devices benefit from the effects of operating at the microscale with microliter and nanoliter volumes of liquid. However, it is a great challenge to load such a small biological sample onto the microfluidic device, particularly for operation outside of a laboratory (the 'world-to-chip' interface challenge). A sample can easily be hundreds of times the volume required and must be accurately deposited in the correct area of a microfluidic device. Furthermore, once inside the device, cell and protein constituents of real-life samples can cause issues such as cells clogging microfluidic channels and proteins fouling sensor surfaces. There is also the technical need to allow for variability in samples (e.g. viscosity, ionic concentration, cell density and debris, analyte concentration, etc) between patients, and from different sample types from the same patient. Biological samples need to be processed to remove cell debris and reaction inhibitors, and to concentrate analytes prior to analysis, through procedures that must be tailored to the target analyte, sample type and most probably the assay itself. Sample processing in microfluidic devices, is therefore a remaining challenge in the development of POC NAAT devices.

Context in which testing is offered

Testing healthcare settings outside of specialist health services

Expanding testing for STIs, HIV, HBV and HCV to healthcare settings outside of specialist healthcare services can be used to target key populations and interventions, such as young people and pregnant women. Such healthcare services include primary care, emergency departments, contraception and emergency contraception clinics and termination of pregnancy clinics amongst others. Nonetheless, in some countries in Europe, such as the Netherlands, primary care is the main setting for STI management [88–90].

HIV testing is leading the way in moving testing to venues other than specialist sexual health or infectious disease services. The long asymptomatic period and the impact of late diagnosis on mortality and cost have led to innovations aimed at diagnosing infections early. These include testing in primary care, emergency departments and other healthcare venues, use of opt-out (i.e. universal offer policies), POC screening tests and use of non-invasive biological samples. Access to HIV testing in primary care is variable across Europe, from countries with no HIV testing in primary care through to countries where policy revolves around primary care based screening [19]. In France, HIV testing should be offered to all adults and adolescents attending primary care facilities, irrespective of behavioural, clinical or demographic characteristics [91]. Modelling data from France suggest that one-time voluntary HIV testing in addition to current practice would be cost-effective at a level considered acceptable by French standards, as would more frequent screening in specific high-risk populations [92]. Following a change in HIV testing recommendations in the UK to include a universal offer of testing to all adults newly registering in general practice in areas with diagnosed HIV prevalence of greater than two in 1 000 population, pilots have demonstrated this approach to be feasible, acceptable and effective at identifying previously undiagnosed individuals [93].

HIV testing in acute care settings, including emergency departments and medical admissions, gives the opportunity to test individuals who may not present at other clinical services [19]. Evaluation data on the implementing of universal, non-targeted HIV testing in emergency departments in several European countries have been reported. Data from 29 emergency departments in Paris, France, found 27% of eligible patients were offered rapid HIV screening, of whom 63% accepted and 61% were tested. New HIV diagnoses were made in 0.14% (n=18) of those tested, however only one patient did not belong to a high-risk group [94]. Further data from Paris, France looking at testing over a longer period of time (up to 12 months) in six Emergency Departments indicates that the offer rate decreases with time from implementation, and is also lower for female patients and those of an older age [95]. Data from UK pilot studies implementing universal HIV testing found emergency department and acute admissions units (serving populations with high prevalence of diagnosed HIV) to be effective, and to identify a positivity of greater than one diagnosis per thousand tested (deemed to be the cost-effective threshold in the United States) [93]. Pilot data from Spain however have found a lower positivity in a similar study (personal communication, J Casabona Barbarà). There remain, therefore, differences between studies on the effectiveness of screening in emergency departments which is likely to depend on both the prevalence in the population served by the department, other testing services provided to that population and sub-groups within it and the coverage of the offer of HIV testing as well as uptake.

Targeting testing to patients presenting with diseases which are potential indicators of HIV infection is being piloted across Europe through HIDES (HIV indicator diseases across Europe study). The conditions and diseases currently identified as indicator diseases in HIDES are sexually transmitted diseases, malignant lymphoma, cervical or anal dysplasia or cancer, herpes zoster, HBV or HCV, ongoing mononucleosis-like illness, leukocytopenia or thrombocytopenia and seborrheic dermatitis/exanthema. HIV positivity in patients presenting with each of these conditions is unknown, but is anticipated to be higher than that of the general population. The aim of the HIDES is to determine in which of these conditions positivity exceeds one in 1 000 (as a marker for potential cost-effective screening), as well as exploring operational issues such as feasibility and acceptability, barriers and data capture [96].

A targeted approach is considered necessary for effective HCV screening in primary care [97]. Testing for HCV in primary care was found to be suboptimal in the United States, even after patients completed and presented to their clinician a questionnaire of HCV risk factors against which they had indicated those that applied. The study found only 8% of 578 patients who acknowledged having a HCV risk factor were tested for HCV in the next two months [98].

Primary care and other healthcare services outside of specialist sexual health, including contraception and reproductive health services, are key settings for the UK opportunistic National Chlamydia Screening Programme (NCSP) [99]. A systematic review of interventions aimed at increasing chlamydia screening in primary care found significant increases in testing of females through programmes that included provision of urine collection pots at registration, linking screening to cervical screening, computer alerts (prompts) for clinicians, internet-based continuing medical education and free sexual health consultations. Programmes which included providing urine collection pots to patients at registration, and clinicians offering tests to all presenting young male patients prior to consultation, have been found to increase testing rates in males [100].

Testing through community settings

Targeting individuals for STI screening, most notably for chlamydia and HIV, in the community, has been both studied and implemented in the form of public health programmes. A variety of venues including pharmacies and locations where target populations gather, such as sports clubs, bars and community events, and services for IDUs have been used [101]. A systematic review of interventions to prevent HIV and STIs in young people in Australia found that those aiming to increase chlamydia and/or HIV testing were more successful when based in non-clinical, non-primary care healthcare settings [102].

A recent systematic review of HIV testing in community settings in resource-rich countries found HIV testing in outreach settings can be successful in diagnosing previously undiagnosed HIV infections in MSM and people from black and ethnic minority groups, and is acceptable to both the target group and staff undertaking the tests [103]. Furthermore, rapid tests increased the proportion of patients who received their result. However, the distinction between populations testing in healthcare and community settings was not clear, and while community testing is providing choice to individuals, the evidence as to whether it facilitates testing of those who would not be tested elsewhere is uncertain. MacPherson et al investigated HIV POC testing in underserved groups through five community-based programmes: a drug-users support group; asylum-seekers health programme; MSM health and support programme; travel clinic; and support programme for homeless people. They found the group that was successfully reached through community-based testing to be more likely to be male, older, of UK African origin and injecting drug users, than those testing in sexual health clinics [104]. For some specific high-risk groups such as female CSWs, both attitudinal barriers (e.g. low perceived risk of infection, stigma) as well as physical barriers (e.g. transport difficulties, registration with health systems) can make conventional venues inaccessible [105].

The HIV COBATEST project has been funded specifically to improve implementation and evaluation of community-based HIV testing in Europe and thus promote early diagnosis specifically in vulnerable and hard-to-reach populations. Initial survey data from participating countries indicate that community-based HIV testing exists in most European countries, with strategic plans and regulation for community-based testing in approximately half of the responding countries. Management, the level of community involvement and performance practices in testing services varied greatly. The majority of countries however have no policy for monitoring the effectiveness of these services [106].

Using pharmacists to offer chlamydia testing is advocated as part of the UK National Chlamydia Screening Programme, [107] and has been piloted in Australia [108]. Furthermore, many pharmacists sell commercial testing kits for STIs both in store and online. A qualitative study by Dabrera et al in London, UK, however found that most pharmacists offered free chlamydia testing only when patients were attending for emergency contraception [109]. Brabin et al conducted a study of home-based self-collection chlamydia screening kits for women presenting to pharmacy for emergency contraception [110]. This study screened 10% of young women requesting emergency contraception but the greatest attrition was due to tests only being offered to 25% of women. Of those women who were offered a test, 46% accepted it and 18% of those submitted a sample. Pharmacists were reluctant to offer testing to women in long-term relationships or who were married and selected patients for testing on the basis of age, education and ethnicity [111].

Outreach chlamydia screening for young people in the UK is not considered to be the most effective approach to screening, leading as it does to large-volume screening of low-risk groups. Outreach work for specific high-risk groups, such as homeless, commercial sex workers, injecting drug users or looked-after young people may be of value where the needs of these groups are not met in more traditional settings [112].

In Australia, one initiative to screen self-presenting MSM attending two gay community events (festival and carnival) following widespread advertisement of the study and using a finger-prick sample in a rapid reactive syphilis test, found rapid testing to be preferred by this self-selected population. Over half of the participants also indicated that they would self-test if the test were available for home-use [113].

Direct access to testing kits and tests

The use of the internet for recruiting young people or other target groups to test for STIs is considered by some to be the most innovative method of offering home-testing; offering convenience and privacy through postal receipt of kits while not limiting the target population by geographical location or the necessity of being registered with a healthcare organisation, school or other list [114]. In addition to public health programmes and studies providing access to STI testing through the internet, there are also fee-based private organisations selling testing and sample-collection kits through the internet, both legally and illegally.

In the Netherlands, the Chlamydia Screening Implementation Programme (www.chlamydiatest.nl) aims to determine whether and how to roll out national chlamydia screening for young people and has used the novel approach of large-scale, systematic internet-based screening. In this programme all 16–29 year olds identified through municipal registers in three pilot areas were sent an invitation letter through the post, together with a unique code giving them access to the website. In the first round of screening 20% of participants requested a test kit and 80% returned a sample. Overall 16% of invitees submitted a sample and viewed their result via the website. A survey of non-responders found that restricted access to the internet played only a limited role in lack of participation, with 77% of non-participants having the internet at home, 13% having access elsewhere and 10% having no access. However, for 9% of non-respondents the lack of internet facilities to check their results privately was a strongly influencing factor in deciding not to participate [115–118].

In the United States, www.iwantthekit.org, based at John Hopkins University, is a website and screening program that provides information about STIs and enables residents from participating areas to request a free home collection kit for chlamydia testing. Overall, approximately 40% of individuals requesting test kits returned a sample [119, 120]. This was however slightly lower in males, with 31% of males requesting test kits returning samples (self-taken urethral swab and urine sample). However, 21% of those tested positive for chlamydia, gonorrhoea or *T. vaginalis*, thus indicating that this approach, in this situation, reached high-risk males [121]. Individuals were asked to wait 14 days before calling a free telephone number for the results. Overall the scale of screening achieved by www.iwantthekit.org was low. Demand for kits was very much associated with the extent of radio advertising, decreasing dramatically when advertising ceased [119, 120]. In the United States and in the UK, internet-requested sampling has been identified as a method for increasing uptake of chlamydia screening amongst men [122].

Internet recruitment has also been used in two schemes in the Netherlands to identify high-risk individuals for syphilis (www.syfilistest.nl) and HCV (www.heptest.nl) testing [123, 124]. MSM were recruited for syphilis testing through online advertisements using online banners on chat (MSM-orientated) and lifestyle sites. A mass-media approach was used for HCV testing recruitment, through regional television commercials, advertisements and online banners. The HCV pilot used a risk-based questionnaire to target the test offer to those individuals at most risk of infection. Both systems enabled users to download a referral letter for an appointment at a testing laboratory of the participant's choice and results were uploaded and accessible through the websites. Among those who downloaded a referral letter, uptake of testing was higher in the HCV testing pilot (28%) than in the syphilis testing pilot (10%). Cost-effectiveness data from the pilots has not been published, but the cost of internet-mediated testing was considered to be low. Each pilot resulted in identifying and getting into care, seven infected individuals; from 898 individuals downloading referral letters and 93 taking up tests for the syphilis pilot and 1 480 individuals being offered a test and 420 taking up the tests for the HCV pilot [123, 124].

Self-testing

Studies have investigated whether patients can and will perform their own POC HIV test [125]. A recent study in Spain showed participants in a street-based HIV testing programme to be able, under supervision of a skilled counsellor, to take a finger-prick blood sample and deposit it appropriately on a rapid HIV test. Such self-collection was considered helpful to facilitate testing using blood samples in countries, like Spain, where only medically qualified staff are legally allowed to take blood samples [126]. A French-based study which recruited patients in an emergency department setting who had already had a standard oral fluid test performed by a healthcare professional, found patients able to collect the sample, run the test and interpret the result. The majority (91%) of volunteers chose the oral-fluid test and 9% the blood test. All but two (from 478) self-test results were concordant with the healthcare professional test [125]. Self-testing for *T vaginalis* by adolescent women, including collection of vaginal swab, running and interpreting the test results, was shown to be as accurate as clinician test results, with all participants running the test correctly and 99% interpreting the self-test result correctly [127]. Another study found self-collection of blood samples and performance of rapid HIV tests by patients to be feasible [126]. Although not the focus of this report, POC CD4 and viral load tests to be used with small readers will become available soon for treatment initiation and monitoring treatment respectively.

Information cascade

Novel ways of recruiting for testing and delivering test results and treatment

It has become common practice in many settings, including STI clinics and national screening programmes, to disseminate results by SMS message. Surveys in the UK and Ireland have found that when asked about preferred methods for providing test results, relatively few young adult patients cite text messaging as the method of choice, with telephone calls and face-to-face contact being preferred [128, 129]. However, evidence from three clinics in London showed that one year after introduction of a service to offer SMS messaging for results, 40% of patients agreed to receive their result by text message [130]. Providing results by text has been shown to considerably reduce the staff time required for giving out negative results and enable management of calls to the clinic as most patients who receive a message stating that their results are now available (sent to patients with a positive result) respond by telephoning the clinic immediately, thus enabling the clinic to direct calls to quieter periods [131]. Studies that have surveyed users after text message receipt of results found the method to be acceptable to patients. In a small study investigating attitudes of MSM to self-taken rectal samples in US San Francisco community venues, where respondents were required to telephone for the results of their tests, only 16% of participants called for their test result despite over half indicating that the telephone was their preferred method to receive the result [82].

In the Netherlands, the pilot evaluations of National Chlamydia Screening require participants to log into a website to participate in screening and to receive their test result. Overall, 96% of respondents, and 97% of chlamydia positive respondents, to a user-survey found the experience of receiving their result via the internet to be good or very good. Those that did not have a good experience reported having forgotten their password or preferring results via telephone call or letter. However, 16% of non-participants reported dislike of the internet as a reason for non-participation [115]. The syphilis and HCV testing pilots from the Netherlands found 97% of those who took up syphilis testing and 95% of those who took up HCV testing logged back on to the relevant website to collect their result [123, 124].

The Cochrane Collaboration recently published a review of social marketing interventions to increase HIV/STI testing uptake amongst MSM and male-to-female transgender women [132]. The report identified only three serial, cross-sectional pre-test/post-test designs (one with a control group and two without), one of which used alert banners on gay websites and one used an internet chat room.

An SMS reminder service implemented at a sexual health clinic in Sydney, Australia, increased the STI/HIV re-testing rates amongst MSM considered high-risk (based on self-reported sexual behaviour) from 31% in the pre-SMS period to 64% in those who were sent an SMS message (714/1 798 HIV negative MSM) [133]. The reminder service also increased re-screening amongst heterosexual men and women diagnosed with chlamydia infection from 21% in the pre-SMS period to 30% in those sent an SMS message (141/343) [134].

Partner notification and treatment

An important and effective component of STI control strategies is partner notification and treatment: indeed, strengthening partner notification has been identified as a pragmatic priority for STI control [89]. Partner notification policies and practices vary across Europe, with partner notification being voluntary in most countries and compulsory in a few [135].

There are a number of examples of internet tools outside of Europe which have been developed with the aim of helping both provider-led and patient-led partner notification [136]. For the provider these include information resources and letter templates, [137] as well as software that can be integrated into clinics' IT systems [138]. For patients, several online tools have been developed that enable them to notify partners free of charge either including their name or anonymously. These sites include www.letthemknow.org.au in Australia, aimed at young people, which offers patients the option to notify partners by email, SMS or letter as well as tips on how to tell a partner face to face. The Australian website www.thedramadownunder.info offers a similar service for MSM to enable partners to be notified anonymously, or with a personal message (email option only). This website also provides a reminder service for registered MSM to inform them when they are due for their next sexual health check-up.

In the United States, www.inSPOT.org is a web-based tool for patient-initiated partner notification which allows users to send e-cards (anonymous or otherwise) to up to six email addresses. This tool was originally developed for a syphilis outbreak in MSM. It was evaluated during its introduction in Colorado, US, through surveys in one clinic mainly catering for heterosexuals (assessing recognition by attending patients of inspot.org and its purpose) and through website-use statistics [139]. This evaluation found that for this population, in this setting, there was no impact of inspot.org. This may be due to the preferences of this mainly heterosexual clinic population, where the majority of patients stated that they would hypothetically inform their partners in person (89%) or via the telephone (37%), with very few indicating they would text (5%) or use email/internet (5%). However, in other settings and other populations, using internet-based partner notification as an adjunct tool where more traditional contact details were not available found it to lead to an 83% increase in the number of sex partners notified of their risk, 26% more sex partners being examined and an 8% increase in number of syphilis cases with at least one treated partner compared to the number that would have been reached using traditional contact information [140].

It may be that for some MSM populations, the use of email and internet-based partner notification is an effective and acceptable, and in some cases the only, method for contacting partners. For some heterosexual populations, notifying partners through email and internet might be less acceptable or used. It may well remain however an important adjunct to other partner notification methods for contacting some partners.

Novel routes for accessing testing and results necessitate innovative approaches to getting those testing positive access to care. Pilots, studies and programmes that have tested patients remotely have approached this differently and requirements will vary depending upon the infection. For example treatment for chlamydia infection can be posted out to participants with positive results but this is clearly not an appropriate or feasible route for patients testing positive for HIV or HCV, where referral to a specialist centre is required.

Novels ways of getting treatment to partners include patient-delivered partner therapy and accelerated partner therapy. There is limited evidence to suggest that treating partners by providing index cases with treatment to deliver can increase the number of partners treated per patient [112, 141–143]. Trials of accelerated partner therapy, whereby access to treatment is via alternative routes (e.g. pharmacy or telephone hotline), are currently underway. Initial feasibility studies showed these methods to be acceptable to patients and to lead to higher numbers of treated partners than traditional partner notification [144]. Patient delivered partner screening, whereby patients deliver testing kits to partners, has also been proposed as a useful tool [145].

Evaluation

Key test characteristics that require evaluation include [22]:

- test performance (sensitivity and specificity)
- performance in specific populations (positive predictive value and negative predictive value)
- ease of use
- conditions of use
- conditions of storage
- shelf-life.

Furthermore, prior to adoption in a specific setting, the impact on the diagnostic pathway includes: ease of biological sample collection; time to prepare sample; time (and hands-on time) to run the test; and turnaround time for results, will also need to be assessed, ideally alongside cost-effectiveness. These evaluations will remain as relevant for new diagnostic devices as for current systems. As testing moves out of traditional laboratory settings and into wider communities where prevalence of infections will differ and there might be limited technical understanding by those conducting the test, a greater importance might need to be placed on predictive values and ease of use. The difficulty of interpreting test results in low prevalence settings is already a challenge: supplementary or confirmatory testing is recommended in the UK for low prevalence populations when the positive predictive value of the gonorrhoea testing algorithm is ≤90% [30], however, in many situations when confirmatory testing is undertaken, defining a true positive case and determining the impact for patient management can be difficult [146].

There are tools available to help professionals evaluate diagnostic tests and decide upon the most appropriate test for their population. These include the web-based interface for evaluation of the tests used by blood donation screening services worldwide [147]. This online model allows decision makers to adapt an economic model of blood screening strategies for their local population. As tests expand into other settings so those individuals making decisions on the purchase of tests expands, moving away from specialists to members of the public, who may not understand the impact on results of tests being used inappropriately e.g. in low risk individuals.

The STARD (Standards for Reporting of Diagnostics Accuracy) initiative has generated guidance on the reporting of studies of diagnostic accuracy [148].

Regulation

The key legislation for the regulation of diagnostic devices in the EU is the Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic (IVD) medical devices and the Commission Decision of 3 February 2009 amending Decision 2002/364/EC on common technical specifications for IVD medical devices [149, 150]. To gain CE marking and thereby permission for marketing across Europe, a device must be assigned to the relevant category based on its purpose; meet the essential requirements as specified in annex 1 of the Directive[2]; and undergo appropriate conformity assessment (which may require involvement of the notified body, depending on the category of the device e.g. for HIV, HBV, HCV and chlamydia) [151].

The essential requirements are primarily concerned with ensuring the device is safe for the user. If a device is for detection of an infection in the high-risk category (List A, annex 2 of the Directive[3], including HIV, HBV and HCV) it must be batch-released by a notified body. Devices are required to achieve, where appropriate, the analytical and diagnostic sensitivity and specificity, accuracy, repeatability, reproducibility (include control of interference) and limits of detection only insofar as claimed by the manufacturer [149]. For the majority of IVD there are no minimum performance standards, such as minimum sensitivity or specificity requirements and no requirement for a clinical validation. The exception is for IVD devices for HIV, HBV and HCV for which the common technical specifications set out the minimum requirements in terms of the number of samples required for determining the performance characteristics (e.g. sensitivity, specificity) claims and acceptance criteria (e.g. sensitivity and specificity required) [150].

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[2] Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. 1998. Available from:
http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/technical_harmonisation/l21010c_en.htm

[3] Available from:
http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/technical_harmonisation/l21010c_en.htm

Self-testing and POC IVD devices also fall under the scope of the European Directive and are additionally required to perform appropriately given the skills and means available to the intended users, and the variation that can reasonably be anticipated in their technique and environment. For IVD devices for the detection of HIV, HBV and HCV this includes the requirement for relevant parts of the performance evaluation to be carried out, or repeated, by appropriate lay users. [150] The regulation of health-related mobile phone apps and websites is currently being debated in both European countries and the USA. [152, 153]

The European Directive for IVD is currently under review, and following a public consultation launched in 2008, a draft revision of the directive is anticipated soon. A key area being considered for review is risk-based classification as promoted by the Global Harmonization Task Force for classifying devices. Currently the categorisation used in the Directive[4] (Lists A (including HIV, HBV and HCV) and B (including chlamydia), annex 2) is effectively static and does not easily evolve as knowledge and technology move forward. Views have also been sought on the need to add specific requirements for POC diagnostic devices, with some respondents suggesting that the manufacturer should be required to show that the device has the same sensitivity and specificity when used in the POC environment as in the laboratory. There was also support for including requirements to demonstrate clinical validity of the device in the Directive, including the positive predictive and negative predictive values. The need to address clinical utility was also consulted upon; where clinical utility includes the requirement to show that the results provide valuable information for the purpose of making decisions about effective treatment or prevention strategies. However, there was little support for this amongst responders. Some responders did however underline that the requirement to demonstrate clinical utility might be of particular interest for direct to customer testing [154].

There is country specific legislation regulating the availability of POC diagnostic devices directly to the public. For example, in the UK, advertising, selling or supplying a home test for HIV is illegal under the HIV Testing Kits and Services Regulations 1992. The sale of kits for home-sampling where biological samples are then sent to a laboratory for testing is not illegal. An enquiry by Medicines and Healthcare products Regulatory Agency (MHRA) in 2007 indicated that the majority of Member States had no specific legislation to prevent the sale of HIV self-test products to the public and hence in some European countries it is legal to sell self-tests for HIV (e.g. the Netherlands). The UK is currently reviewing its policy with a recent House of Lords Select Committee recommending that the law be changed to allow home-testing. This follows several incidences of HIV home-tests bought illegally over the internet being found to be dangerously inaccurate [155].

Quality assurance and quality control

Quality control (QC) of the production of commercially available diagnostic tests is regulated by CE-marking under the European Directive 98/79/EC and requires batch-release by a notified body for some devices, including those for the detection of HIV, HBV and HCV [149]. This QC ensures that devices are safe and that performance of devices remains as claimed by the manufacturer when applying for CE marking. Quality assurance (QA) and QC of the testing facilities are not regulated at the European level. European countries may have their own accreditation scheme, such as Clinical Pathology Accreditation (CPA) (UK) Limited, the organisation responsible for the UK's External Quality Assurance (EQA) schemes. This organisation runs EQA schemes for microbiology and virology laboratory accreditation and also provides an EQA scheme for POC testing facilities (not self-testing by patients). This POC testing scheme is not compulsory and must be linked to an accredited laboratory.

Point of care tests are obliged to have an internal control to determine that the biological sample used was sufficient and that the test ran successfully. The specification, and substrate (e.g. water, serum etc), of the internal control will differ between tests. The requirement to read this control output together with the sample output to interpret the result (e.g. two lines) is well established and used in other home-testing kits including pregnancy tests.

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[4] Available from:
http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/technical_harmonisation/l21010c_en.htm

4. Discussion and conclusions

Public health impact

These novel approaches to testing have the potential to improve access to, and hence uptake of, testing among individuals and population groups at risk, decrease the turnaround time between testing and results and hence, for bacterial STIs particularly, increase the proportion of infected individuals treated earlier in infection as well as overall. At a population level, and depending on how these technologies are deployed, decreasing the duration of infectiousness and the coverage of treatment may in turn reduce transmission, clinical consequences of infection and, if testing and treatment levels are sufficiently high, potentially lead to a reduction in incidence and prevalence of infection. For HIV and other viral STIs including hepatitis, greater access to testing enables earlier access to care where (earlier) treatment and health promotion could decrease the risk of onward transmission, as well as reduce morbidity. For novel technologies, this may be particularly important for the serocoversion periods for HBV, HCV and possibly HIV infection.

The additive and synergistic effects of using new testing technologies together with modern information and communication systems enables the development of novel testing pathways in current settings where testing is undertaken as well as expansion of testing to new community-based settings. Point of care testing is becoming an increasingly popular method over standard laboratory testing for diagnosis of infectious and genetic diseases. Changes to the testing pathway itself could improve throughput of patients and thus increase testing and treatment rates as well as access. So far, HIV rapid testing in clinics has been shown to increase the proportion of clients receiving results in some settings, compared to conventional HIV tests [19]. The option of using non-invasive biological sample types for some tests, such as self-taken vaginal swabs, urine, finger-prick or oral fluid, may also increase test uptake and could decrease clinician time. It is not known at this point how any concomitant decrease in clinical examinations or microscopy would impact on patients' outcomes.

The most promising technologies for POC testing are based on nanotechnology and microfluidics. These have the potential to control both the complex fluidic handling required during sample processing and the reagent mixing for nucleic acid amplification, in areas which are separated spatially and temporally, while being compatible with inexpensive materials and fabrication methods [156]. The technologies are rapidly progressing towards 'sample-in answer-out' platforms for molecular diagnostics. However, nanotechnology and microfluidic approaches are not without their challenges, in particular, allowing for the variation in source clinical material and heterogeneity that exists within biological sample types. Sample preparation remains a bottleneck in the development of a truly fully integrated and automated handheld device for POC testing. Interfacing sample collection devices with testing devices (and sample preparation) also remains a major challenge that will need to be overcome before the full benefits of POC molecular diagnostics can be reaped.

Testing for STIs, HIV, HBV and HCV outside of specialist sexual health services, both in healthcare and non-healthcare settings, offers the opportunity to increase testing uptake in populations at high risk of infection through increased choice of testing venue and by reaching those who might not otherwise access testing. Testing for HIV and chlamydia have led the way in expanding testing provision in these types of settings. Universal testing policies (i.e. irrespective of risk, also referred to as opt-out testing), use of POC testing devices and acceptable sample types have all encouraged uptake of HIV testing in these settings. Further targeted testing strategies, for example through community services for high-risk groups such as commercial sex workers or MSM have been successfully employed. For chlamydia, opportunistic screening through healthcare and non-healthcare settings in the UK, and pilot programmes that recruit participants through the internet in the Netherlands have screened 25% of the target age group in the UK programme and 16% in the Netherlands pilot. The use of rapid tests for HIV has been shown to increase the proportion of patients who receive their result, as well as being acceptable and accessible for participants. This may be of particularly importance in community settings, which are frequently targeting hard-to-reach or transient groups.

Expanding testing into community-based settings, and particularly expansion of home-testing, will see the decision-making for test selection move away from clinical pathology specialists and towards non-experts. CE marking offers no guarantee that a test is of clinical utility, which requires full evaluation of a test in the population that will use it [157]. Given an array of tests to choose from and without an obligation for manufacturers to clearly present performance characteristics, nor a full understanding of these characteristics by purchasers, individuals are likely to purchase a test based on other factors, such as cost and marketing. There could potentially be negative consequences from the lack of requirements for the accuracy of tests to be demonstrated in, and by, populations being tested prior to marketing. For example, tests used may lack sensitivity or users may lack understanding of the limitations of a test (for example, during the window period after HIV infection, when an individual is at their most infectious). These factors could have serious negative consequences including enhanced transmission as well as clinical consequences. Available tests may also lack the required specificity increasing chances of over-treatment and mis-diagnosis of still stigmatized illnesses. Specificity is particularly concerning for technologies that are deployed in low prevalence settings and in which confirmatory testing is not available. There will likely be large benefits from increased access to testing through community-based, and eventually home-based, testing but clearly these benefits will only be reaped if the tests used are accurate in the populations undergoing testing.

Tests currently available and tests likely to be available in the foreseeable future for use in community settings and home-testing do not provide comprehensive STI screens, but rather detect one or two infections (primarily HIV testing or chlamydia and gonorrhoea). The impact of such selective testing on infections that are not included in the test is unknown. This will likely depend on the extent of co-infections and treatment-pathways for the detected infection and whether these include any more comprehensive screening; the natural history of infection (e.g. infections that are mostly asymptomatic might be more affected than frequently symptomatic infections); the prevalence of infections in those taking up testing; and perhaps most importantly, any risk-behaviour or behaviour change that ensues following the test result.

Adoption of novel approaches to testing, including testing and communication technologies and any subsequent changes in the testing pathway and policies (e.g. targeted versus general testing), will impact on cost and cost-effectiveness which will also be dependent on other factors and likely differ for different infections and populations. Changes that increase uptake of testing, and subsequent treatment, of individuals at risk of infection that lead to a decrease in the pool of infection (decrease in the proportion of individuals infected and in the average duration of infection), would be beneficial. But these will need to be weighed up against the costs of novel technologies and new testing pathways, any loss of sensitivity or specificity, and adverse impacts of the novel technologies (e.g. lack of impact on other infections, changes in risk-behaviours, etc) compared to conventional testing and pathways. The expansion of testing among lower risk individuals with a lower prevalence of infection will reduce the positive predictive value of any test and thus increase the number of individuals with false-positive results and the subsequent adverse effects of such a diagnosis. The perspective taken for cost-effectiveness analysis will be important as the burden of costs, rather than reducing, could move from one provider to another, or to individuals.

Adaptation of data sources for surveillance, and of surveillance systems themselves, are likely to be necessary as testing moves out of traditional, centralised facilities and into disseminated non-clinical testing venues and eventually home-testing. In settings with currently limited surveillance systems this offers the opportunity to embed surveillance mechanisms from the outset, while in countries with established systems, complementary systems or adaptation of existing systems are likely to be required. Home biological sample collection strategies should not pose too many challenges for surveillance which can be routed through central testing laboratories similarly to many current systems. However, home testing will present a new challenge, especially for self-contained tests, such as lateral flow devices, which do not require any connection to a central server or the internet to run the test or interpret results.

Areas with little evidence to guide policy and practice in Europe

Data are beginning to accumulate with regards to the benefits and implementation of different testing strategies, for example the higher uptake of opt-out versus opt-in HIV testing. There remain however gaps in the evidence on the benefit of, and optimum methods for, implementing testing for many infections in non-specialist settings, and how testing strategies are best balanced across a range of settings, to gain the greatest public health impact.

Some key questions remain around the feasibility of testing in non-specialist settings for different infections and the use of different tests (and combinations of these), including which non-specialist testing settings should be used, who should offer and perform tests, who will fund testing and follow-up, how acceptable and popular such testing will be with the public and how to implement and maintain quality assurance and quality control of these programmes. As home-testing becomes a reality, similar issues will arise with regard to how they should be used, both at a strategic level, for example how they can be integrated with, and complementary to, other testing programmes and healthcare systems, and by the individual, for example what are the most appropriate and acceptable biological samples, how to ensure accurate interpretation of results, data security (and perceived data security) and how to enable access to clinical care pathways.

There is little evidence currently available on how modern communication technologies and tools, including the internet, smart phones, apps and social media, can best be used to increase testing, retesting and health promotion for those at risk of infection and treatment and partner notification for those testing positive.

Whether there is any impact of novel approaches to testing on behaviour will be important to understand and is currently unknown. Two aspects of behaviour could feasibly be altered with the availability of novel testing approaches i) test-seeking and uptake behaviour and ii) risk behaviour. The impact of widely available self-testing kits can only be speculated about at this stage. It is very feasible that impact could be both positive and negative from a public health perspective. For example, widely available self-testing kits for chlamydia could increase uptake and frequency of chlamydia testing in young, sexually active asymptomatic populations, and this could both improve chlamydia control and free up time in healthcare settings, such as specialist STI clinics, for more frequent attendance by individuals at highest risk of other infections. A negative impact however might see the widely available, but limited tests replace full sexual health screens for those at highest risk and hence facilitate the spread of less common, particularly asymptomatic infections. The impact of self-testing on sexual behaviour is unknown. It will be important as early POC and self-testing technologies become available and testing programmes begin to be implemented, to determine whether changes in behaviour are a real issue and the impact they could have.

Tests targeting multiple infections are being developed for POC use, for example chlamydia with gonorrhoea and HIV with syphilis. There is currently a paucity of data to inform the optimal combinations of tests, and any pay-off that might be required between increased breadth of testing and decreasing sensitivity or specificity for each component. Technology advances (micro- and nano-technology) are likely to continue to increase the number of targets that can be tested for using a single biological sample. There are both technological and public health implications of widening the scope of tests on which evidence will be required. From the technology perspective, ensuring that the inclusion of multiple targets does not impact on the sensitivity and specificity associated with each individual infection, for example through interference or competition in the assay, is clearly important. Consensus on the regulatory requirements for multiplex tests is needed, particularly where the separate components have been previously approved individually. From the public health perspective, it will be necessary to determine whether it is appropriate to test populations for a number of infections including ensuring acceptable positive predictive values for each one, that the results inform management or behaviour changes and that there are routes into clinical care pathways for each potential diagnosis.

Community-based testing is as yet undefined and it remains to be agreed whether it should be defined by the population being tested or by the organisation offering the test. An agreed definition would help structure, and hence articulate, the evidence, discussion and recommendations around community-based testing.

Recommendations

Research priorities for novel technologies for HIV, HBV, HCV and STI testing are broad ranging and include:

1. Models, or frameworks, for strategic, evidence-based decision making on adoption of novel approaches to testing.
2. Technology adoption type reviews of novel technologies and approaches, clearly defining the benefit and potential route to large-scale adoption in European countries of particular approaches. In addition to facilitating roll-out of important technologies, such a system would also encourage innovation by providing an evident translational pathway for industry.
3. Operational research on the best methods to implement testing programmes for different infections, and combined testing. This includes aspects of programme structure, such as setting, testing technologies (in light of the target population and real-life performance of the test), quality control and assurance, as well as programme management and the use of modern communication technologies.
4. Improving capability of the technical aspects of testing devices. Examples include, improved detection of infections (e.g. reducing the window-period for detection of hepatitis infections as part of blood screening, improved tools for syphilis diagnosis), developing technologies for easy collection and transfer of biological samples into micro- and nano-technology testing devices and development and regulatory approval of combined tests (e.g. combined syphilis and HIV tests).

Activities that could be undertaken at European level to ensure maximum public health benefit from novel approaches to testing fall into three main areas. As evidence accumulates on the most effective methods for implementing testing in different settings and employing novel technologies, it is important that this is consolidated and reviewed, and that evidence-based guidance on testing approaches, including operational matters, is generated in a timely manner. This includes incorporating national testing strategies into a European-wide strategy. These activities can be included in current projects on HIV testing and chlamydia control strategies.

It could be considered to support implementation and evaluation of novel approaches to testing across Europe by developing models, or frameworks as appropriate, to facilitate strategic, evidence-based and structured decision making on their adoption. Whilst the outcomes from such models or frameworks are likely to differ between countries, given the variation in populations and healthcare systems, the questions that need to be addressed to ensure considered implementation of new approaches to testing will remain similar.

Guidance, support and capacity-building need to be provided for surveillance and of testing for these infections, to enable the development of surveillance systems that will remain fit for purpose as novel testing technologies are further adopted, including community-based HIV testing, other POC tests and home testing. High-quality surveillance systems will enable countries to monitor trends in infections and testing, and potentially assess the impact of interventions.

Appendix 1 – Literature search criteria and results

Scientific literature broad search criteria (search conducted using Pubmed)

	((near[Title/Abstract] AND ("patients"[MeSH Terms] OR ("patients"[MeSH Terms] OR "patients"[All Fields]) OR ("patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields]))) OR ("point of care"[Title/Abstract] OR "Point-of-Care Systems"[MeSH Terms]) OR ((rapid[Title/Abstract] OR (real[Title/Abstract] AND ("time"[MeSH Terms] OR "time"[Title/Abstract]))) AND "test*"[Title/Abstract] OR ("diagnosis"[MeSH Terms] OR "diagnos*"[Title/Abstract])) OR ("screening"[Title/Abstract] OR "mass screening"[MeSH Terms] OR ("mass"[Title/Abstract] AND "screening"[Title/Abstract]) OR "mass screening"[Title/Abstract]) OR "biomedical technology"[MeSH Terms] OR ("technology assessment, biomedical"[MeSH Terms] OR "technology assessment"[Title/Abstract]) OR "device approval"[MeSH Terms] OR "device approval"[Title/Abstract] OR (conformite[Title/Abstract] AND (europeenne[Title/Abstract] OR europeene[Title/Abstract]) OR ("CE"[Title/Abstract] AND "mark"[Title/Abstract] OR "marking"[Title/Abstract]) OR "food and drug administration"[Title/Abstract] OR (("Clinical Laboratory Improvement Amendments"[All Fields] OR CLIA[All Fields]) AND waiver[All Fields]))) AND ("humans"[MeSH Terms])
AND	("Diagnostic Techniques and Procedures"[majr])
AND	(((("sexual behavior"[MeSH Terms] OR "sexual*"[Title/Abstract]) AND ("infection"[MeSH Terms] OR "infection"[Title/Abstract] OR "communicable diseases"[MeSH Terms] OR ("communicable"[Title/Abstract] AND "disease*"[Title/Abstract]) OR "communicable diseases"[Title/Abstract])) OR ("chlamydia trachomatis"[MeSH Terms] OR ("chlamydia"[Title/Abstract] AND "trachomatis"[Title/Abstract]) OR "chlamydia trachomatis"[Title/Abstract] OR "neisseria gonorrhoeae"[MeSH Terms] OR "human papillomavirus"[Title/Abstract] OR "HPV"[Title/Abstract] OR "hiv"[MeSH Terms] OR "hiv"[Title/Abstract] OR "hepatitis b"[MeSH Terms] OR "hepatitis b"[Title/Abstract] OR "hepatitis c"[MeSH Terms] OR "hepatitis c"[Title/Abstract] OR "treponema pallidum"[MeSH Terms] OR ("treponema"[Title/Abstract] AND "pallidum"[Title/Abstract]) OR "treponema pallidum"[Title/Abstract] OR "syphilis"[MeSH Terms] OR "syphilis"[Title/Abstract] OR "herpes simplex"[MeSH Terms] OR ("herpes"[Title/Abstract] AND "simplex"[Title/Abstract]) OR "herpes simplex"[Title/Abstract] OR "trichomonas vaginalis"[MeSH Terms] OR ("trichomonas"[Title/Abstract] AND "vaginalis"[Title/Abstract]) OR "trichomonas vaginalis"[Title/Abstract] OR "mycoplasma genitalium"[MeSH Terms] OR ("mycoplasma"[Title/Abstract] AND "genitalium"[Title/Abstract]) OR "mycoplasma genitalium"[Title/Abstract] OR "vaginosis, bacterial"[MeSH Terms] OR ("vaginosis"[Title/Abstract] AND "bacterial"[Title/Abstract]) OR "bacterial vaginosis"[Title/Abstract] OR "lymphogranuloma venereum"[MeSH Terms] OR ("lymphogranuloma"[Title/Abstract] AND "venereum"[Title/Abstract]) OR "lymphogranuloma venereum"[Title/Abstract]) OR (("chlamydia trachomatis"[MeSH Terms] OR ("chlamydia"[Title/Abstract] AND "trachomatis"[Title/Abstract]) OR "chlamydia trachomatis"[Title/Abstract]) AND (serovar[Title/Abstract] OR L1[Title/Abstract] OR L2[Title/Abstract] OR L3[Title/Abstract]))))
AND	("2009/01/01"[PDAT] : "2012/01/01"[PDAT]))
AND	("humans"[MeSH Terms])

Grey literature search

Search terms used to search, using google.co.uk	HIV testing point of care, Novel HIV testing technology, Novel STI testing technology, STI point of care tests, hepatitis B testing technology, hepatitis C testing technologies, STI diagnostic testing, trichomonas testing technology, syphilis testing technology, herpes simplex testing technology, gonorrhoea testing technology
Specific website additional searches	NICE, ECDC, WHO, UNAIDS

Conference abstracts searched:

- ISSTDR (The International Society for Sexually Transmitted Diseases Research) 2009 and 2011
- ECCMID (European Congress of Clinical Microbiology and Infectious Diseases) 2010, 2011 and 2012

Terms used included – testing, diagno*, point of care, HIV, hepatitis, syphilis, herpes, HSV, HPV, papilloma*, gonorr*, chlamydia, trichomonas, mycoplasma, LGV, treponema, sex*, communic*, internet

Where * indicates an abbreviated term was used.

Glossary

Agglutination methods: These tests consist of a test card or microscope slide onto which the biological sample and the agglutination solution which contains analyte-specific detector molecules are added. When the analyte is present, agglutination (clumping of particles to form insoluble aggregates) can be observed [1].

Avidity testing: Avidity is a measure of the strength of binding of immunoglobulin G antibodies to an antigen [2]. The avidity of IgG increases over a period of months following initial infection, and avidity tests use this property to identify new infections (i.e. antibodies with low-avidity) [3].

E-health (electronic-health): E-health is defined by the World Health Organization as the transfer of health resources and health care by electronic means, and includes i) the delivery of health information through the internet and other telecommunications methods for both healthcare professionals and consumers; ii) using IT and e-commerce to improve public health services (e.g. through education and training of health workers) and iii) the use of e-commerce and e-business practices in health systems management [4].

Flow-through test: This test is based on the flow of biological sample fluid through a porous membrane and into an absorbent pad. The analyte is captured on the surface of the membrane by analyte capture molecules and, after a wash step and addition of the signal reagent, and further wash stage, the result can be read [1].

Lateral flow tests: (also called immunochromatographic strip tests or simply strip-tests), simple-to-use tests that rely on capillary flow to move the biological sample, together with the solubilized detector molecules, from the sample pad up through the membrane until it reaches the analyte capture molecule (a second line of antibody or antigen, immobilized as a thin stripe in the nitrocellulose which then captures the complex if it is positive for the target analyte, and a control line) [1].

M-health (mobile-health): A sub-field of e-health, m-health is the use of mobile communications (e.g. personal digital assistants (PDAs) and mobile phones) for health services and information [5].

Micro and nano technologies: Micro and nano refer to the scale of components of the technology: a micrometre is 10^{-6}m and a nanometre 10^{-9}m.

Non-amplified antigen detection: Any method that detects antigens of infections without amplification of the nucleic acid, for example by agglutination, flow-through or lateral flow tests.

Nucleic acid amplification technologies (NAATs): in-vitro methods to increase the number of copies of a nucleic acid (DNA or RNA) sequence in a sample prior to detection.

Solid-phase immunoassay: immunoassay in which the antigen or antibody is bound to a solid surface (dipstick). In most examples, the dipstick is placed in the specimen solution, washed, placed in the detection agent solution and washed again before reading (a visible spot) [1].

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