Public Health England

False positive treponemal (syphilis) IgM enzyme immunoassay results:
Adverse incident report

About Public Health England

Public Health England's mission is to protect and improve the nation's health and to address inequalities through working with national and local government, the NHS, industry and the voluntary and community sector. PHE is an operationally autonomous executive agency of the Department of Health.

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Published October 2013
PHE gateway number: 2013278

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1 Summary

This report outlines in some detail the problems encountered in a number of laboratories with false results in one of the tests used for diagnosis of recent syphilis infection. The reasons behind these false results are explained. The root causes have been identified and recommendations made to reduce the likelihood of recurrence. The report of necessity contains many technical terms, and is aimed at a healthcare audience.

Where recommendations refer to the HPA these recommendations now apply to its successor organisation, Public Health England.

Syphilis remains an important sexually transmitted disease, not least in England where the incidence of infection has been increasing year-on-year since 1997. In the early stages of infection the diagnosis can be made by detection of the bacterium *Treponema pallidum* in material from the primary ulcerative lesion by dark ground microscopy or by polymerase chain reaction, both tests with high specificity from lesions in genital sites. After this primary stage of infection the treponemes disseminate throughout the body and produce the symptoms of secondary syphilis. The infection then enters a latent phase, where there are no clinical symptoms. Progressive disease may manifest with the symptoms of late or tertiary syphilis up to 30 years after the initial infection. At all stages, except in the very earliest presentations of primary syphilis, the principal diagnostic tool available for diagnosis is antibody testing. This approach, in use for over a century, is complicated by the need to use both treponeme-specific and treponeme-nonspecific tests to determine both the presence of infection and whether it is active.

In recent years IgM antibody testing for syphilis, as a stand-alone test and/or combined with IgG testing, has been introduced to help bring serological diagnosis to an earlier point in primary syphilis and as an adjunct to assessment of activity. However, as with all serological tests bringing high sensitivity, and in particular IgM tests, there can be problems of specificity; such tests should always be confirmed by a full serological profile of tests and follow-up tests on later blood samples as well as clinical assessment. A treponemal IgM test was in use at a number of laboratories, including a Health Protection Agency (HPA) reference laboratory, which gave an even higher rate of nonspecific results than expected. Although isolated IgM results were reported generally with a comment to interpret with caution, some clinicians acted on these, resulting in the misdiagnosis of patients as having early infection when they did not and in the wrong staging of infection in some individuals, leading to inappropriate treatments.

In addition to the need to resolve the laboratory test problem, once the adverse clinical outcomes were recognised it was decided that it was necessary to undertake a major look-back exercise to identify individuals possibly affected by clinical actions based on the false positive laboratory results. Thus, separate look-back and laboratory investigations were undertaken, and the recommendations made at the conclusion of these are reported.

Overall root causes have been identified, and recommendations to rectify those made.

1.1 Identification and scale of the problem

The HPA Sexually Transmitted Bacteria Reference Laboratory (STBRL), Colindale, identified an unexpected increase in positive treponemal IgM results using the Mercia (Microgen Bioproducts) Syphilis M kit. STBRL subsequently alerted the manufacturer, who issued an alert letter to users, and the HPA reported the problem to the Medicines and Healthcare products Regulatory Agency (MHRA), which promptly issued a device alert.

Three batches of the test kit were subsequently found to have generated excessive numbers of false positive results between November 2010 and September 2011. These unsatisfactory batches of a commercial enzyme immunoassay for treponemal IgM antibody were used in eight UK laboratories (including two in the HPA). In total, 3,342 samples from 1,941 patients from over 50 NHS trusts had tested positive with the affected batch kits.

1.2 Incident response

The incident was declared a Level 3 incident. An HPA incident control team (ICT), including senior HPA and NHS personnel, public health, genitourinary medicine and microbiology professionals and colleagues from the devolved administrations, was established in October 2011.

Two sub-groups were convened; one to co-ordinate a patient notification (or ‘look-back’) exercise, and the other to review laboratory processes. The Executive Group and Senior Management Teams were updated regularly.

1.3 Review of laboratory processes

A full review of laboratory practices, including interviews and vertical audit at Colindale and Birmingham laboratories, was conducted. These identified no particular problems in laboratory processes at either site, or in the handling of the incident.

Quality systems in place were felt to be fit for purpose, and both were commended for procedures and controls in place. Some minor recommendations were made for future resilience, for example, early warning mechanisms such as generation of exceedance scores, tracking drift in negative IgM results, and innovative reporting methods.

Algorithms have been developed for PHE laboratories to risk stratify diagnostic assays in use to ensure rigorous quality assurance processes are in place.

There are ongoing discussions regarding the revised algorithm for syphilis testing to replace the withdrawn former V44.

Investigations are underway into collecting a panel of staged syphilis sera, which will allow easier validation of syphilis tests.

The HPA is in the process of reclaiming the costs of additional test kits used by STBRL.

Recommendations

- revise and agree the syphilis testing algorithm to emphasise the limitations of IgM testing, with more defined scope for its use
- comments on laboratory reports need to highlight test parameters to a greater extent to reflect the limitations of IgM testing
- consideration should be given to whether the scope of external quality assessment (EQA) schemes should be expanded to provide a more robust means of assessing laboratory performance of treponemal IgM testing
- obtain and implement the use of a panel of staged syphilis sera to validate syphilis tests throughout the various stages of syphilis infection
- roll out algorithms for HPA laboratories to risk stratify diagnostic assays
- a guideline for validation and verification of assays in serology should be established in the HPA, similar to that established for molecular assays. This should be published as a standard method
- some standardisation of kits might also be desirable within HPA laboratories, where there is currently great variation
- consideration should be given as to whether some of the former working groups, for example the syphilis network, should be re-established. Such groups might be useful to allow exchanges about assay performance, allowing data to be shared and discussed at an early stage. The Clinical Services and Public Health Delivery Group is another group where early concerns about assays might be raised and that group is willing to take on that remit

1.4 Look-back

The look-back team decided that patients meeting certain criteria should be contacted. These criteria reflected whether the patients' management had changed as a result of a positive result, either by being incorrectly treated for syphilis, or incorrectly treated for an earlier stage of disease.

A phased approach of clinical review of patient care by NHS trust staff and repeat testing was undertaken.

More than 95% of the affected positive samples were followed-up through this phased approach (3,180/3,332). However, there were 152 samples from patients where NHS trusts were not able to provide information on whether the faulty test kit result had changed the clinical management of the patient, either due to the patient being lost to follow-up, or to clinicians not responding to the investigation. These samples were retested and microbiologists and trust medical directors were then informed by letter of these patients and their results, ending the HPA's investigation and returning the onus of ongoing investigation to local management.

Results of retesting indicated an IgM false positivity rate of 96% in samples with only a single positive IgM or one other positive test in the syphilis-testing panel. For those samples with multiple positive results, the false positivity rate of the IgM test was 68%.

The results of the retesting and clinical review identified 40 patients who required contacting. This represents 2% (40/1941) of patients who had originally tested positive with the affected kits. Of these 40 patients, 25 are known to have been misdiagnosed and 15 are known to have been undertreated.

A co-ordinated approach for directly contacting patients through their clinicians was undertaken and guidance materials for NHS trusts were prepared by the ICT. There was proactive media engagement.

It is known that 27 of the 40 patients have subsequently been successfully contacted.
The HPA remains aware of only one instance of complaint, a contact of a patient who has requested an apology from the NHS trust. Many patients were reported to have been relieved to be followed-up and to have their management corrected.

The HPA received positive feedback via an online questionnaire from clinicians and microbiologists on the handling of the incident.

HPA teams worked well together across divisions; however, the look-back exercise was resource intensive on ICT members, laboratories (especially STBRL) and NHS trusts.

Recommendations

The following should be considered when undertaking large public health look-back exercises of this nature:

- identify sufficient information officer resource when large and/or complex data handling is involved
- involve permanent members of staff where possible for additional experience and exposure to complex incidents
- use shared IT facilities, eg email, shared storage spaces
- involve the legal department at an early stage
- prospectively record the additional work taken on, eg count hours, to identify opportunity costs of the incident management
- ascertain clear lines of accountability
- clarify early on with senior teams, such as the National Executive and Senior Management Teams, what their expectations are for situation reports and briefings, including agreed timing, content and format
- for long incidents, aim to include more than one person to fulfill each role in the incident control team, where possible
- involve local health protection teams early when a prompt local response is needed to national incidents

- if time allows, allow a period of reflection about significant decisions
- for complex incidents requiring a non-acute/critical response from many external agencies, expect many delays and build these into realistic timeframes for milestones
- when requiring a significant response from acute trusts, communicate early and directly with the medical director
- pilot protocols with clinicians/staff not intimately involved in the incident

1.5 Root causes

The primary root causes for the incident are listed below together with key recommendations and proposed actions.

Root cause 1: There is insufficient understanding of the regulatory framework relating to the quality and clinical utility of commercial serological assays.

Root cause 2: There are deficiencies in quality assurance systems for certain laboratory assays.

Root cause 3: Algorithms for test selection and use may not be sufficiently clear or prescriptive.

Root cause 4: Existing established governance processes for dealing with suspected test performance issues in a timely fashion may be underutilised.

Root cause 5: Clinicians may act on laboratory results in inappropriate ways.

Root cause 1

There is insufficient understanding of the regulatory framework relating to the quality and clinical utility of commercial serological assays.

CE marking may be regarded as a quality mark and give a false reassurance about the robustness and efficacy of clinical laboratory tests. The CE marking may be taken to imply safety and conformity to the manufacturer's intended purpose for the assay, and to assessed quality standards, but does not necessarily imply the highest standards of sensitivity or specificity for clinical laboratory diagnosis.

The regulatory framework for safeguarding 'the health of the public by ensuring that medical devices work and are acceptably safe' provides no power to require manufacturers of raw materials to divulge to the competent authority to which other manufacturers those materials have been supplied.

Recommendations

- there is insufficient understanding of the limitations of the CE marking process; what the CE mark stands for in terms of assay performance should be more widely known
- senior PHE personnel should arrange a meeting with MHRA to discuss issues around the regulatory framework and how they might be improved
- the importance of adequate verification of commercial assays when introduced into a laboratory should be further stressed; validation of commercial assays is often quite limited. Examination of evidence of appropriate verification of assays and of ongoing quality assurance should be a standard part of laboratory accreditation assessments
- PHE experts should compile a guidance note on validation and verification of serological assays (similar to that recently written for molecular assays). It should be published as a Standard for Microbiology Investigation on the PHE website

Root cause 2

There are deficiencies in quality assurance systems for certain laboratory assays:

- some assays may not have optimal verification due to lack of suitable samples
- some assays may not be adequately quality controlled when in use because of the absence of a national external quality assurance scheme, or because of the lack of material for regular internal quality assurance checking
- if assays regularly pass their run validation criteria and do not fail Westgard rules it may be difficult to recognise at an early stage an unexpectedly high false result rate
- a strengthening of the process for early identification of greater numbers of reactive results than expected is desirable
- samples referred to reference laboratories may have inadequate clinical information and limited information on the local test results that led to referral. This can make it more difficult to recognise results obtained by the reference laboratory that are inconsistent with the clinical presentation, potentially leading to delays in identifying a problem with a test

Recommendations

- approach the National External Quality Assessment Service (NEQAS) to request additional IgM testing within the existing treponemal IgM scheme where sample numbers allow

- a national serum bank should be set up to store samples from rare and relatively uncommon conditions, including samples representative of different stages of infection that can be made available for test validation, verification and ongoing quality assurance. For syphilis, this would allow the creation of a bank with useful numbers of samples from primary infection, where IgM testing is most useful

- PHE experts should compile a guidance note on validation and verification of serological assays (similar to that recently written for molecular assays). It should be published as a Standard for Microbiology Investigation on the PHE website

- exceedance criteria should be ascertained for all serological assays to allow early recognition of changes in pattern of results

- reporting of test results should, where staffing permits, be arranged so that there are periods of continuity in reporting by one individual for one test area, allowing easier recognition of trends in results

- laboratories should maintain regular dialogue with clinical colleagues to discuss changes in local patterns of infection such as syphilis, and should regularly refer to national epidemiological information resources to identify changes

- reference and referral laboratories should further encourage referring laboratories to include the results of the initial testing and the clinical information with the referred specimen

Root cause 3

Algorithms for test selection and use may not be sufficiently clear or prescriptive. This may lead to unintended consequences when laboratories provide a rapid service to reduce turnaround times for panels of tests to a minimum. For example, a test might be done simultaneously with other tests rather than as a reflex test following earlier test results. These unnecessary tests have the potential to lead to over-interpretation of individual reactive results.

Testing algorithms try to give guidance on acceptable standards of testing and confirmation. They can be difficult to frame when they attempt to cover what follows

after differing approaches to screening, leading to lack of clarity. The treponemal testing algorithm V44 in use at the time of this incident is an example where the role of IgM testing at different stages of infection was not well defined.

Recommendations

- published algorithms and guidelines, including those from specialist societies and the Standards for Microbiology Investigations available on the PHE website, should be clear on the need for confirmation of tests and give clarity on appropriate testing models, particularly where appropriate tests may differ at different stages of an infection
- laboratory standard operating procedures should always include clear reporting criteria and comments compatible with the advice in published peer-reviewed national guidance

Root cause 4

Existing established governance processes for dealing with suspected test performance issues in a timely fashion may be underutilised.

- laboratory meetings do not always lead to documented actions with timelines for review, and may be restricted to small numbers of staff in reference laboratories
- clinical audits are undertaken by the laboratories, however, they may not provide the full picture about whether patient management is affected by test result interpretation
- although there is a process for alerting senior staff external to the laboratory or within the governance structure of PHE to a potential issue this could be further clarified and defined
- there is a lack of written guidance on further defined actions to take, for example, further testing and communication with other laboratories when suspected test performance issues arise
- concerns about the performance of an assay may not be raised promptly because of some uncertainty as to the validity of the concerns, especially in the face of manufacturer or distributor doubts of any problems. In addition, laboratory staff may be wary of reporting concerns over assay performance to MHRA until they have a substantial amount of data, delaying the process. This results from a misperception of the role of MHRA, which should be involved at an early stage so that a body of information can be gathered in one place to inform the scale of a problem, the manufacturer can be contacted, and consideration given to an investigation

Recommendations

- meetings of laboratory staff should be held more regularly, preferably weekly, to allow discussions of possible problems
- enhance the procedure to ensure that concerns about assay performance are reported to senior staff at an early stage regardless of feedback from the test manufacturer. A suggested appropriate forum would be a regular laboratory quality meeting where external and internal quality assessment (EQA and IQA) and general test performance are reviewed
- for laboratories within which specialised services function to some extent independently, and where services are provided from more than one site, there is a need to have local quality meetings in each area and, in addition, frequent laboratory/centre-wide quality meetings, thus allowing a broader scrutiny of potential problems. Such meetings should always include medical staff so that potential risks to clinical patient management and public health are discussed in a wider forum and not underestimated
- clinical governance arrangements for reference laboratories should ensure that there is regular medical as well as scientific review at all stages of the testing pathway, with both medical and scientific input into defining the quality parameters within which complex serology is performed
- clear guidance as to when a deviation from the expected pattern of test results would trigger the involvement of expert medical and scientific assessment at an early stage
- reassurance from a kit manufacturer that an assay is performing satisfactorily outside the laboratory where concerns have been raised should not delay wider investigations and discussions with other laboratories using the test
- formal networks of interest groups among PHE laboratories should be established to provide regular exchange of information on particular topics in laboratory diagnosis, including areas such as syphilis, blood borne viruses and testing in the immunocompromised. The creation of such regular, formal meetings will facilitate ad hoc informal contact with colleagues at an early stage when problems are suspected
- MHRA should be informed at an early stage when an assay deficiency is suspected, in line with PHE policy

Root cause 5

Clinicians may act on laboratory results in ways that do not take account of caveats expressed in the interpretive comments associated with reported results due to insufficient dialogue between clinicians and laboratory personnel.

Recommendations

- increased opportunities for dialogue between laboratory and clinicians should be sought, including joint educational meetings
- further education and training in the area of interpretation of syphilis serology and its pitfalls should be available, especially for junior clinical staff
- national clinical management guidelines (such as ‘UK National Guidelines on the Management of Syphilis 2008’) should have strengthened sections on syphilis serology, including discussion about the possibility of false positive results as well as false negatives

2 Introduction

This report provides a full update report of investigations into the increase in false positive syphilis IgM results at eight UK laboratories arising from three faulty batches of a particular brand of treponemal IgM EIA kit (the Mercia Syphilis M kit manufactured by Microgen Bioproducts) which led to a small number of individuals being incorrectly diagnosed with syphilis, or incorrectly treated for an earlier stage of infection.

3 Background

3.1 Syphilis serology

In England and Wales, less than 200 laboratories perform approximately 1.5 million syphilis tests per annum (900,000 sexual health and 600,000 antenatal screens). Seven regional HPA laboratories perform primary diagnostic and confirmatory testing on 200,000 of these samples. STBRL performs approximately 10,000 tests per annum.

The screening algorithms for syphilis are complex and nuanced, as many laboratory tests are used to provide a composite picture of the likelihood of recently acquired, established, or treated disease.

Algorithms list IgM testing as part of a confirmatory strategy. National guidelines are a consensus of expert opinion on the role of IgM in the algorithm. There is, however, no universal standardisation, and the use of only one type of serologic test is insufficient for diagnosis because each type of test has limitations, including the possibility of false-positive test results in persons without syphilis. Treponemal IgM testing is used in the diagnosis of early syphilis and congenital syphilis. National and STBRL algorithms in use at the time of the incident are listed in Appendix 3.

Additional tests used include rapid plasma reagin (RPR), *Treponema pallidum* particle agglutination assay (TPPA), and enzyme immunoassays (EIA) detecting total treponemal antibodies (EIA Total). In line with national algorithms, results of such assays are not usually reported without interpretive comments and the results of other assays. Most IgM reactive results were reported with comments indicating the exercise of caution in interpreting their significance. A fuller review of syphilis testing is included in Appendix 4.

3.2 Identification of the problem

An unexpected increase in positive treponemal IgM results was noted at the HPA Sexually Transmitted Bacteria Reference Laboratory (STBRL), Colindale, without any concomitant increase in reports of acute clinical cases (Appendix 1).

The increase in IgM positive or equivocal tests rose between November 2010 and September 2011 from the baseline average of seven IgM-only reactive results per month to an average of

35. This was not due to increased testing, as the proportion of positive tests concomitantly increased. Three batches of the Mercia (Microgen Bioproducts) Syphilis M kit had generated excessive numbers of false positive results from November 2010.

STBRL alerted the manufacturer to the problem and the company issued an alert letter to users on 24 August 2011, pointing to problems with two batches. The HPA reported the problem to the Medicines and Healthcare products Regulatory Agency (MHRA) on 14 October 2011 including information on a third affected batch (Appendix 2). This resulted in MHRA issuing a Medical Device Alert MDA/2011/104 on 3 November 2011.

3.3 Scale of the problem

Eight UK laboratories used the affected kits; two of the laboratories were HPA laboratories, and of the remainder, two were in England, three in Scotland, one in Wales. Referring laboratories were based in the UK as well as one laboratory in the Republic of Ireland and one in Gibraltar. In total, 53 hospitals were involved.

Table 1: Number of patients testing positive or equivocal with the affected IgM EIA kit, the Mercia (Microgen Bioproducts) Syphilis M, batches 052x1, 053x1, 05411a at laboratories who used the kit

Laboratory	No. of patients testing positive or equivocal
HPA Colindale (reference laboratory)	1,423
HPA Birmingham (reference laboratory)	130
Royal Free Hospital, London	284
St Thomas' Hospital, London	16
SNBTS, Glasgow	5
Ninewells, Dundee	8
New Royal Infirmary, Edinburgh	140
PHL Wales, Cardiff	53
TOTAL	**1,941**

3.4 Potential consequences of incorrect test results

It became apparent from initial discussions with clinicians, alerted by STBRL about the incident, that some clinics did use the IgM test results to make diagnoses of early syphilis in a small number of individuals, resulting in unnecessary treatment.

There were also some individuals with confirmed syphilis infection who may have been undertreated because of misinterpretation of the stage of disease due to the reactive IgM test. STBRL laboratory was the most affected because of the large number of samples tested, almost all of which were referred as reactive samples from screening elsewhere.

4 Incident response

The incident was declared a Level 3 HPA incident and was reported on the Incident Reporting Information System (IRIS) on 12 October 2011. HPA led this incident for England, but colleagues from Scotland and Wales also took advice from the HPA look-back team.

A national incident control team (ICT) led by HPA Microbiology Services was convened to investigate this issue in October 2011 with the strategic aim of exploring the reasons why a test that has significant inaccuracies was used and to ensure that the technical problem was corrected, any impact on clinical care was identified and steps were taken to help avoid a similar problem in future. Membership included senior HPA and NHS personnel, public health, GU medicine and microbiology professionals and colleagues from the devolved administrations.

A subgroup of the ICT, the look-back group, led by HPA Health Protection Services was tasked to co-ordinate any patient notification required, with the aim of redressing the impact on patients of any incorrect results. This was to identify and inform patients that may have had their management changed by false positive results from particular batches of the Mercia syphilis IgM kit (052x1, 053x1, 05411a). It was agreed that patients were to be notified only if they were given an incorrect diagnosis of syphilis or if their clinical management was affected (through under-treatment). Patients whose clinical management had not changed or been affected by the laboratory results would not be notified.

A second subgroup was charged with laboratory investigation at both STBRL and HPA Birmingham.

The terms of reference and membership for each group are listed in Appendix 5.

Two trainees were identified to support the investigation.

Updates were provided to the Department of Health, British Association for Sexual Health and HIV (BASHH), devolved administrations, antenatal screening programme, sexual health programme boards, MHRA, National External Quality Assessment Service (NEQAS) and European Centre for Disease Prevention and Control (ECDC).

The timeline for meeting dates and incident deadlines is detailed in Appendix 6.

5 Laboratory investigation

5.1 Laboratory review

As part of the investigation into excessive false positive treponemal IgM results with the Mercia syphilis M EIA, a group was tasked with visiting the HPA laboratories affected by the issue—Birmingham HPA laboratory at Heartlands Hospital, Birmingham, and STBRL at Colindale, London (fuller review detailed in Appendix 11). Both laboratories were visited although the whole team could not be assembled for either visit.

Both laboratories were working to high standards. Both held full Clinical Pathology Accreditation (CPA) and had evidence of satisfactory quality systems. There was little to criticise in either laboratory, with few non-compliances against CPA standards.

The test that led to the problem of syphilis over-diagnosis and misinterpretation was the Mercia Syphilis M test, an enzyme immunoassay for the detection of *Treponema pallidum* specific IgM antibodies in human serum. This is an IgM capture assay in which human serum IgM antibody is captured by rabbit anti-human μ chain antibody coated on the wells of the EIA plate. Purified horseradish peroxidase labelled *T. pallidum* antigens are captured by *T. pallidum* specific IgM and the addition of tetramethyl benzidine (TMB) substrate results in a colour change which is stopped by addition of sulphuric acid. The optical density is then read with a spectrophotometer at a wavelength of 450nm. The validity of each test run is determined by the results of a cut-off control, a positive control and a negative control. Specimen results are interpreted by their results in terms of an antibody index, the ratio of mean absorbance of the sample to the mean absorbance of the cut-off control. Failure to meet any of the validation criteria (cut-off control absorbance between OD 0.200 and 0.600, positive control index >2, negative index <0.7) invalidates the test run.

Sera are considered positive for treponemal IgM if the antibody index is >1.1, negative <0.9, equivocal between 0.9 and 1.1.

Interpretation of results requires care. The manufacturer reminds users that the diagnosis of an infectious disease should never be based on a single test result, but should take account of clinical history, symptoms and serological data. For diagnosis of primary or recurrent treponemal infection testing of paired sera is advised. The IgM assay results may be influenced by non-treponemal antibodies in sera containing ANA, EBV IgM, Borrelia IgM and parvovirus B19 IgM.

The manufacturer also highlights the performance characteristics of the test, with the caveat that a negative result cannot exclude recent treponemal infection. Specificity of 100% is stated, based on testing 100 TPPA negative samples from pregnant women, and of 99% based on testing 90 TPPA negative samples from blood donors. In the specificity calculation equivocal results were scored as true negative. This appears to be at odds with the interpretive table, which does not suggest that equivocal results are negative, but rather advises further testing. If the equivocals were included in the specificity calculation, the specificity for the test in pregnant women would be 98%. Diagnostic sensitivity in 83 samples with IgM reactivity detected by FTA-Abs was 97.4% (again taking equivocal results as negative). Among the samples tested, 11 (13%) were from primary infections, 17 (20%) secondary, two tertiary and five were

reinfections. Among sera from individuals with latent infection, 11 of 52 (21%) were reactive in the Mercia IgM assay compared with 28 (54%) reactive in the FTA-Abs 19S IgM assay.

Although STBRL ran the V44 syphilis serology algorithm somewhat differently from most laboratories, there were rational reasons for doing this. The use of IgM testing as a frontline assay fitted in with technical and operational flows in the laboratory and addressed the need to reduce turnaround times for complete testing. It fitted with the fact that essentially all samples received at STBRL are referred there after initial reactive test results at a primary testing laboratory.

Similarly, Birmingham used the IgM assay extensively because of doubts about the sensitivity of their frontline EIA (Abbott Murex ICE) in detecting treponemal antibody in early treponemal infection, a frontline assay that could not be changed easily because of an ongoing process to move serological assays into a blood sciences track facility.

For STBRL, with its high ratio of referred samples, it may be that more initially reactive sera are being sent than previously. Modern automated EIA platforms in primary testing laboratories may be producing more false reactive EIA results than in the past. STBRL suspected that this might be a problem with Abbott Architect, but the rate of false IgM results on samples initially screened by Architect is commensurate with the usage of the platform—it is the market leader. Newcastle has drawn attention to an increase in false reactivity with Siemens and Roche screening tests on automated analysers.

5.2 Laboratory conclusions

Excessive treponemal IgM reactive results were generated in two HPA laboratories through use of a commercial kit, the Mercia Syphilis M EIA, three batches of which did not perform satisfactorily. The problem was flagged up to the supplier by both laboratories. The company initially suggested that no other laboratories had reported that there might be a problem with the kit. Birmingham stopped using the test because of regular failures of the kit to meet its run validation criteria. At STBRL use was prolonged because there was no clear failure of the assay and no breach of internal quality control (IQC) monitoring rules. There was, however, an identifiable increase in the number of positive IgM results being reported.

Although IgM testing is not advocated in the algorithm published at the time nationally (V44) there may be a lack of clarity as to its place in testing outside the neonatal period. The two laboratories were unusual in having used IgM testing early in their local testing algorithms, for differing but justifiable reasons. STBRL used it early because almost all of their samples were referred, so had already had screening tests done and were often of small volume. Birmingham had a lack of confidence in their screening test but could not change the initial test at that time because of planned reconfigurations to serology testing.

The national algorithm needs to be rewritten to emphasise the limitations of IgM testing. In addition, comments need to reflect these limitations. Comments on STBRL reports were generally cautious, particularly with regard to isolated reactive IgM reports. It was disappointing to see how often the caution with which the laboratory viewed its results and reported them was not translated into a similar cautious approach by some clinicians. The use by STBRL of a comment that differed somewhat from that suggested by V44 may have contributed to this clinical approach in seeming to emphasise the possibility of ‘acute’ rather than ‘active’ infection.

However, it seems that, in general, there is a gap in understanding between laboratory and clinician about the characteristics of some tests, including the positive and negative predictive values as well as absolute sensitivities and specificities. Reports may need to highlight test parameters to a greater extent.

The type of problem seen here is quite difficult to recognise early. For the most part the assay runs passed the criteria for validity in STBRL. In Birmingham, the problem was greater with full test run failures occurring such that the laboratory withdrew the kit and introduced another (Mikrogen).

For many assays an increase in reactivity rate may not be flagged by external quality control systems, which are infrequent relative to the routine sample testing and so tend to detect gross problems only. They are also unlikely to be noted on internal quality assurance because the original result is likely to be reproducible with the same assay and IQA is usually done soon after receipt of a sample so the same batch of kit is likely to be used. The problems were not picked up early in either HPA laboratory by routine internal quality control value monitoring.

An EQA scheme for syphilis serology is available through UK NEQAS. However, its capability to provide robust assessment specifically of treponemal IgM serology is limited. The difficulty in obtaining sufficient plasma from individuals with recent syphilis infection limits the inclusion of true IgM positive specimens, and thus the sensitivity of each laboratory's IgM testing cannot meaningfully be assessed. Furthermore, individual laboratories may not undertake IgM testing, and even if they do, they may not apply the test to the EQA samples. Consequently, the capability of a general treponemal serology scheme to identify relatively subtle changes in a particular manufacturer's diagnostic device is limited. An EQA scheme whose focus is treponemal IgM serology may be more effective; UK NEQAS should consider the utility and feasibility of this.

This same source of material from early cases should form the basis of a bank of sera containing representative samples from large numbers of cases of treponemal infection at all stages of infection, primary, secondary, latent, and tertiary. This material would be available for validation and verification of treponemal antibody kits coming in to use. Validation and verification are difficult in serology in the absence of sufficient samples of the right type at the various stages of infections. Commercial assays are often validated on relatively small numbers of samples.

A guideline for validation and verification of assays in serology should be established by PHE, similar to that established for molecular assays. This should be published as a standard method. Some standardisation of kits might also be desirable within PHE laboratories, where there is currently great variation.

The length of time taken by STBRL to express concerns might be criticised, although there are good reasons why the recognition of the problem was difficult. STBRL approached the problem in a satisfactory and systematic way. There was little or no hard evidence for some time of a kit problem, and investigations of all the relevant laboratory systems were undertaken, including the change to setting up the test manually. It had seemed likely that some of the test problems might have been due to the DS2 machine, which had been giving problems, and this led to an increased use of manual testing.

One reason why this situation persisted, aside from reassurance from the supplier, was that it was reasonable to believe that the rise in positive IgM results reflected a genuine increase in sexually transmitted infection in the STBRL catchment area. This was entirely plausible because it coincided with a significant rise in diagnosis of lymphogranuloma venereum in the area. It is fair to say that there was a suspicion that the test was not performing accurately but an unwillingness to highlight the problem to MHRA with little evidence. Discussions about possible problems took place with the manufacturer who initially claimed that no other laboratories using the test were having a problem; it later became clear that there were problems in other laboratories with these kit batches.

There were no formal or informal networks within HPA where ‘gut feeling’ concerns about assay performance could be considered or where data could be shared and discussed at an early stage. The disbandment of a number of network groups, for example the HIV Diagnosis Forum and the Syphilis Forum, contributed to the lack of data and information sharing within HPA laboratories.

Consideration should be given as to whether some of the former working groups should be re-established to allow such exchanges. Alternatively, a network teleconference on a regular basis might fulfil some of these aims. The Clinical Services and Public Health Delivery Group is another group where early concerns about assays might be raised and that group is willing to take on this remit.

The MHRA has legislative power to oversee the manufacture of commercial assays, including the quality standards of subcontractors to a manufacturer. However, MHRA does not have power to obtain information about which kits contain particular raw materials. The identification of test failures due to a raw material quality failure must come voluntarily. This leaves a risk that kits using the same raw materials as kits that are identified as flawed are able to remain in use. In the case of the Mercia IgM test, the root cause lay with faulty reagents from a supplier. However, the raw materials supplier is not obliged to divulge other users of faulty materials to MHRA, who in fact have a duty of confidentiality to commercial suppliers.

MHRA acted promptly within its powers once notified of the problem. Involvement of MHRA at an early stage might have reduced the impact of the false reactivity.

An algorithm has been produced for laboratories to risk stratify diagnostic assays in use in order to ensure that rigorous quality assurance processes are in place across all PHE laboratories.

5.3 Potential reasons for high levels of initially reactive screening tests

Each hospital that referred samples to STBRL was asked to identify which screening test they used as part of the investigation into why so many referring primary diagnostic laboratories had excessive rates of false reactivity.

Of 43 laboratories (~2000 samples) referring to STBRL, all but two screened with a total EIA. Forty-four per cent used the Abbott Architect platform: by NEQAS returns Abbott is the leading immunoassay provider (45% of NEQAS 2959). This accounted for 55% of samples tested, so the Abbott platform’s representation is compatible with its market share. Therefore no

automated platform appears to be less specific, though all have high false positivity rates (Table 2).

Table 2: Reactivity in initial screening test for referred samples testing positive or equivocal with affected batches of the IgM EIA kit

Total EIA Antibody Kit Manufacturer	Numbers of samples	Proportion of referred samples (%)
Other non-EIA screening	79	4.2
Abbott	1035	54.7
ADVIA Centaur® Syphilis (SYPH)	6	0.3
Biokit Bioelisa 3.0	221	11.7
Bio-Rad	200	10.6
Bio-Stat	87	4.6
Immulite	122	6.4
Lab21	123	6.5
Newmarket	10	0.5
Treponostika: BioMerieux	9	0.5
Total	**1892**	**100**

6 Look-back

6.1 Rationale for contacting patients

The first part of the look-back was to identify patients whose clinical management was changed by a potential false positive result.

The look-back team considered that clinical management would only have changed in a minority of cases with false positive results. However, only by a process of local clinical review and re-testing was it possible to identify how many patients were affected.

The look-back group decided that a patient notification exercise was needed for patients that met ALL the criteria in Table 3. Patients whose management was not affected by a false positive result did NOT meet the criteria and were NOT contacted. This decision was undertaken following lengthy discussion, and it was felt that it was important to correct mistakes - even if a small number of patients were ultimately affected - due to duty of care, as well as organisational reputation and confidence in service provision.

Two groups of patients were recognised to potentially be affected; those with only IgM reactivity (+/- one other test), where the concern was misdiagnosis and mistreatment, and those with multiple reactive tests. These individuals may have been misdiagnosed and unnecessarily retreated, but could also have been diagnosed with early versus latent disease and therefore been undertreated, eg one penicillin injection versus three, or two weeks of doxycycline versus four.

Table 3: Criteria for notifying patients. Patients must have met ALL 3 criteria		
1	They had a likely false positive IgM result	Defined as a reactive Mercia IgM kit result with the above batch numbers AND a non-reactive IgM from a validated kit from a different manufacturer (eg Lab21, Mikrogen). The only exception was the minority who did not have enough stored sample to retest: as the false positivity of the remainder was ~95%, it can be assumed these would likely also have a non-reactive IgM from a newly validated kit.
2	They were given a diagnosis of syphilis	
3	The IgM result changed their clinical management in one of three ways	They were given a diagnosis of syphilis and/or offered and/or received treatment OR they were treated for an earlier stage of syphilis than they would have if the IgM result had not been positive, resulting in undertreatment, ie receiving a shorter course of treatment OR they could have been unnecessarily retreated following repeat testing after a further exposure, if they had existing markers of syphilis.

A co-ordinated, phased approach was taken for patient notification, listed in Appendix 7.

Phase 1: Investigations identified which patients met the criteria completed by 23 January 2012 with feedback to the ICT.

Phase 2: All affected patients were to begin to be contacted on 13 March 2012 by their clinicians using standard developed materials provided by the ICT and supported by a communications plan.

Phase 3: All remaining patients were identified in the two months following 13 March 2012, with retesting of any additional patients in the first week of May, and subsequent notification. All existing samples where the patient outcome had not been identified were then retested and the relevant hospitals and chief executives informed.

6.2 Retesting of specimens

For the specimens tested at the HPA laboratories, it was decided to retest all those that may have contributed to a false diagnosis of syphilis. The criteria were: treponemal IgM only reactive or treponemal IgM reactive with reactivity in one other syphilis test only, using affected batches of IgM Kits. This retesting was completed by 23 December 2011.

Retesting of 717 samples from the HPA reference laboratories with an alternative IgM kit identified that 96% of the original results were false positives. Given the extremely high rate of

false reactivity, it was decided that where samples were insufficient to retest, their initial IgM results would be regarded as false (Table 4).

A proportion of samples from patients who had two or three other tests positive, in addition to the IgM, were retested to provide a better estimate of the likely false positive rate and to inform amended laboratory reports for affected patients. In February 2012, 50 samples were retested and the false positivity rate of these samples was found to be 68% (Table 5).

Table 4: Reference laboratory re-testing of IgM only (+/- on other result) samples

Reference laboratory	No. samples met re-test criteria	No. insufficient	No. re-tested	Re-test result +ve	Re-test result equiv.	Re-test result -ve	% False +ve
STBRL	640	62	578	13	2	563	97%
Birmingham	149	10	139	7	1	131	94%
Total	**789**	**72**	**717**	**20**	**5**	**692**	**96%**

Table 5: Reference laboratory re-testing of random selection of multiply reactive samples

Type of sample	No. re-tested	Re-test result +ve (True +ve)	Re-test result equiv.	Re-test result -ve	% False +ve
Samples from patients who on initial testing had two or three other positive tests in addition to the positive IgM	50	16	0	34	68%

6.3 Overview of the look-back process

After the reference laboratory retesting was completed at the HPA reference laboratories, a co-ordinated, phased approach was taken. All microbiologists from primary diagnostic laboratories who referred samples to these laboratories were notified of these results (by 23 December 2011). The microbiologists were asked to work with sexual health and other clinicians to identify those patients whose clinical management was affected by a false positive result.

The microbiologists were sent a list of patients potentially affected by 23 December 2011 using a standardised proforma, including clinician and GP contact details. The look-back team contacted those laboratories with more than 50 affected patients to support and clarify what was expected. They were provided with guidance materials and were asked to complete their investigation and report back the outcome by 23 January 2012. A clinical review of notes and results was needed to see if any of the patients met the criteria. If treatment was given, or the patient was otherwise adversely affected, for example with undue worry or concern over the test result, this was recorded on the accompanying template (Appendix 8). For STBRL this involved contacting 44 hospitals, with a further nine from Birmingham. The maximum number of results that individual microbiologists and clinical colleagues had to review was 351 (range 1-351).

Where there was insufficient sample to re-test, the only way of clarifying the diagnosis was to request a further sample from the patient: this was tackled at the patient notification stage. Any patient who may have been undertreated or retreated as a result of a Microgen IgM test kit result had their sample re-tested by the reference laboratory using two different kits (Lab21 and Mikrogen). Those who may have been misdiagnosed had their sample retested with one further kit (Mikrogen), as they had already been retested using the Lab21 kit.

The six other primary diagnostic laboratories, which used the affected kit batches, were also asked to complete their investigations to identify patients whose management was changed by a false positive test by 23 January 2012. These laboratories had flexibility in how they identified patients meeting the above criteria.

A further 83 samples potentially affected by the faulty kit batches were identified during the finalisation of the initial patient contact phase. These had been omitted from the original hospital review due to an incorrect cut-off date on the STBRL access database query. Further satisfactory confirmatory checks were conducted to ensure that all patients were identified. These samples came from 42 patients who had not previously been investigated - all hospitals were subsequently contacted with details of these new patients, ranging between one and six patients at each site. No new hospitals were affected, and this was a relatively minor addition to the nearly 2,000 total number of patients to be investigated.

6.4 Security of Information

While working with clinician colleagues to identify the above information, microbiologists needed to ensure that patient identifiable information was secure. Emails sent between the ICT and microbiologists were encrypted. The same encryption client was used to securely return relevant data to the ICT.

Responsibilities around information governance provided to microbiologists and clinicians included:

- ensuring clinicians were only advised of results relevant to their own patients
- reminding clinicians that emails cannot be assumed to be secure when sent outside of their own NHS organisation and that emails from nhs.net accounts are only secure if sent to other nhs.net accounts
- confirming that information should be sent to the ICT using the Volt secure email client data
- avoiding printing of patient identifiable information unless absolutely necessary, and shredding this immediately when no longer required
- not transferring patient data to other storage devices such as unencrypted memory sticks
- remembering that as with any other laboratory data, they were responsible for its security once they had received it

6.5 Patient contact

The initial planned date for a co-ordinated patient notification was 20 February 2012, but was changed to 13 March 2012 to give hospitals more time to complete their investigations and to ensure that all samples from affected patients were retested.

On this date clinicians from all affected sites were contacted with the results of the retesting and asked to start contacting affected patients, using standard letters and Q&As developed by the look-back group (detailed in Appendix 9).

However, if clinical need dictated, clinicians were asked to inform patients earlier should there be any possibility that waiting for the co-ordinated response would lead to a delay which could have an impact on their health, for example, if antenatal patients needed additional treatment during their pregnancy.

Patients were contacted by their treating physician. In the majority of cases, this was expected to be the GUM clinician. If the GUM clinician was not initially involved in their care, then the treating physician was advised to involve them. GPs were informed where possible, but it was expected that in a high proportion of cases, GUM clinicians did not have permission to share clinical details with the GP.

The following principles applied:

- patients were contacted in a co-ordinated manner on the same date making use of standard materials, including Q&As
- they were offered a discussion with a suitably experienced GUM clinician
- a communications plan was in place
- clinicians were recommended to contact affected patients initially by telephone, and to offer all these patients a face-to-face appointment to discuss these issues, if needed
- template letters were available to clinicians if they were unable to contact the patient by telephone and they decided that writing to the patient was the most appropriate form of communication, given its confidential and sensitive nature

6.6 Communications

The HPA was the national communications lead for this incident. A communications plan was shared with communications teams in the affected hospitals and enquiries about this were directed to the national communications lead, the HPA chief communications officer.

A proactive press release embargoed until 13 March 2012 was distributed on 12 March to all national and medical trade media, and was placed on the HPA website. This press release received coverage from BBC News Online and the Press Association, with short articles in several Scottish nationals and the ‘i’ version of The Independent. The director of STBRL was interviewed for BBC Radio Scotland.

Other communications included liaison with NHS Direct, the National Screening Committee, BASHH, the devolved administrations, and internal HPA briefing notes to affected health protection units (HPUs).

6.7 Results of look-back investigations

The overall response rate was very high - of all the samples that tested positive using the affected batches of kit, 95% were followed up to identify whether the IgM result changed the management of the patient (Table 6).

Table 6: Number of samples from patients with outcomes fully investigated

Centre	Samples testing positive	No follow up	Proportion complete
Royal Free Hospital*	284	1	99.6%
St Thomas Hospital	45	0	100.0%
Dundee*	8	0	100.0%
SNBTS*	5	0	100.0%
Edinburgh	230	0	100.0%
HPA labs	2,760	151	94.5%
Total	**3,332**	**152**	**95.4%**

*number of patients used, other figures relate to number of samples

6.8 HPA results

All 53 hospitals that were affected by the testing at the HPA laboratories responded in part or in full. HPUs and medical directors of strategic health authorities (SHA) were contacted to support and encourage the referring laboratories that had not responded either completely or partially by the 23 January 2012. The vast majority of hospitals (50 out of 53) completed or nearly completed their investigations in time for the initial co-ordinated patient notification on the 13 March 2012.

Of all the samples that tested positive using the affected batches of kit, 96% were followed up to identify whether the IgM result changed the management of the patient.

Twenty-three hospitals identified 78 patients whose clinical management had likely been affected by the initial incorrect IgM results. These samples were retested using two separate kits. Of these, 70 samples met the criteria identified by the HPA for consideration of patient contact.

Patient contact commenced on 13 March 2012 after completion of retesting of all linked samples from patients identified by clinicians who had their management changed by potential false positive IgM results. The results on retesting were notified to the microbiologists, with simultaneous electronic release of the retest results and amended comments. Detailed instructions for onward communication with relevant clinicians and patients, along with template notification letters and comprehensive FAQs, were also distributed. Microbiologists were followed up to ensure they understood the accompanying materials.

The incident team followed up the outcome of all of these patients with the appropriate GU physician and microbiologist. After further clinical review by the clinicians, approximately half of the patients (33) required contacting. Of these, two-thirds (21) were misdiagnosed and one-third (12) were undertreated. In 11 cases, the trust had not been able to contact the patient due to a number of reasons; changes in country of residence (some have returned home eg to Eastern Europe), inability to reach patients, or where the patient simply did not wish to be seen again, even for further treatment. Overall, this represented approximately 2% of patients whose samples were affected by HPA reporting.

The HPA remained aware of only one instance of a complaint (a contact of a patient who requested an apology from the trust). Many patients were relieved to be followed up and told about the incident and the potential for false positive results.

6.9 Non–HPA results

For the six non-HPA laboratories that used the test, all but one completed their investigation in time for the initial patient notification on 13 March 2012.

The Royal Free Hospital laboratory had 941 patients tested with the affected kits, of which 284 had previously tested positive. Of these, 196 were possible false positives. Of these 196, one antenatal patient was identified as being treated in labour, as a result of a false positive. Two other patients were potentially affected; unfortunately there were no stored samples for these patients and therefore they could not be retested. One was advised to present to GUM due to the possibility of syphilis infection, and was retested and found negative. The other, who divides his time between the UK and India, was undertreated. They have been unable to contact him, but he is due follow up in a renal clinic and a copy of the letter was sent to his renal physician. Nine other samples from patients at Queen Elizabeth Woolwich (QEW) hospital were tested at the Royal Free and were subsequently found to be negative. None were treated based on the incorrect IgM result. QEW was informed directly of these results.

St Thomas' Hospital tested 45 samples from 44 patients, and identified 11 samples from 10 patients that were potentially false positive. On re-testing one was a true positive and one was equivocal, and the remainder were false positive. Clinical review indicated that no patients had treatment or had a change of treatment on the basis of the false positive IgM results alone.

The Scottish National Blood Transfusion Service (SNBTS) in Glasgow identified four patients with IgM results from the affected kit that had been reported as "evidence of treponemal infection". These patients were then referred to GUM clinics. Three were retested at GUM clinics with no effect on management. One was lost to follow-up despite multiple contacts and it was not clear what treatment or diagnosis was given.

Edinburgh Royal Infirmary identified 230 samples from 140 patients that could have been affected by the faulty kit. Forty-one patients retested negative, of whom four were potentially affected (two misdiagnosed, two undertreated) and required further re-testing at the Scottish Bacterial Sexually Transmitted Infections Reference Laboratory (SBSTIRL). Three were negative and were successfully contacted. One 'undertreatment' was lost to follow up due to moving abroad.

Ninewells Hospital in Dundee identified eight patients who were tested with the affected kits but none had any change in management. The Public Health Laboratory in Wales reviewed all relevant patients and no patients' management was affected by this incident.

In total, seven further patients were identified by NHS laboratories, of whom four were misdiagnosed and three were undertreated. Two were lost to follow-up, and the rest were successfully contacted.

6.10 Sample completion

There were 151 samples from patients where the trust was not able to provide information on whether the faulty test kit result had changed the clinical management of the patient, either due to the patient being lost to follow-up, referred out of area, or to clinicians not responding to the local microbiological investigation. These outstanding samples came from a variety of physicians including many GP samples.

All samples were retested to draw a line under the HPA's investigation. Microbiologists and trust medical directors were informed by letter of these patients and their results, ending the HPA's investigation and returning the onus of ongoing investigation to local control.

6.11 Legal Issues

A legal opinion was sought from the HPA Head of Legal Affairs. The manufacturer of the kits could be named as this information was already in the public domain, as long as any reference was not defamatory. Counsel advised that the incident team could seek compensation from the manufacturer for the costs of the defective kits and provided preliminary advice, subject to full legal review, about the cost of retesting. The Executive Group endorsed this course of action, and the HPA approached the company for compensation. Advice was sought from the NHS Litigation Authority for patients seeking recompense.

6.12 Incident conclusion

A letter of thanks from the HPA Chief Executive was sent to all hospitals involved in the incident. The director of STBRL reissued revised reports for all patients whose results fell within the affected period, with support from a microbiology specialist registrar.

6.13 Lessons identified

The incident risk assessment, the laboratory and look-back exercises were complex, requiring public health, medical microbiology and virology technical skills, expert clinical input, cross-divisional and external collaboration.

An incident debrief co-ordinated by the lead for the look-back group and a public health trainee identified lessons learned (see Appendix 12). There were many aspects of the investigation that were identified as having gone well:

- a very high proportion of potentially affected patients were assessed

- as far as possible, all affected patients were contacted (or had contact attempted)
- there was risk mitigation for those patients who could not be followed up
- there was good team working across the various sections of the HPA involved in the response, with fluidity in roles; strong cross-border relationships with colleagues in the devolved administrations; and close liaison with regulatory authorities and the NHS

The key salient points that may inform future exercises were:

- the initial timeframes were unrealistic, with the complexity underestimated. For incidents that require a non-acute/critical response from many external agencies, it is sensible to expect many delays and build these into realistic timeframes for milestones
- clear lines of accountability should be ascertained at the beginning, and the legal department should be involved from an early stage. If time allows, a period of reflection on significant decisions may be beneficial
- when a significant response is required from an acute trust, communicate directly with the medical director. Direct communication with responsible senior management would have provided better levers for completion of the look-back exercise
- it is important to have the right people in the incident group and, where possible, more than one person fulfilling each role for long incidents where they may not be available for every ICT, eg two GUM clinicians
- clarify early on with senior teams, such as the Executive Group and Senior Management Teams, what their expectations are for situation reports and briefings, including agreed timing, content and format
- prospectively record the additional work taken on, eg count hours, to identify opportunity costs of the incident management
- shared IT facilities (email, shared storage spaces) are essential, and earlier use of such platforms would have been helpful, with sufficient information officer resource when large and/or complex data handling is involved
- involve permanent members of staff where possible for additional experience and exposure in complex incidents, as well as piloting protocols with clinicians/staff not intimately involved in the incident
- early involvement of local health protection teams where a prompt local response to a national incident is needed

7 Onward steps

There are several steps that lead on from the conclusion of this investigation:

- the HPA will reclaim the costs of test kits used by STBRL
- a revised algorithm for syphilis testing has been drafted to replace the withdrawn former V44: this has formed the basis of discussions with the director of STBRL and others. The revised final algorithm will be used as the basis for IgM use within the UK
- a panel of staged syphilis sera is required to validate syphilis patients' serological progression throughout the various stages of syphilis infection. Such a panel would be used to assess both existing and novel tests. The sera may be able to be collected as routine monitoring through existing arrangements with GumNet clinics, and this will be further investigated. To begin this process, a presentation was made to a GumNet/GRASP Collaborators Meeting in September 2012
- the lessons learned will be disseminated by submitting the key findings of this report to various microbiology and sexual health conferences
- the algorithms for PHE laboratories to risk stratify diagnostic assays in use will be rolled out across the network

8 Root causes

The primary root causes for the incident are listed below together with key recommendations and proposed actions.

Root cause 1: There is insufficient understanding of the regulatory framework relating to the quality and clinical utility of commercial serological assays.

Root cause 2: There are deficiencies in quality assurance systems for certain laboratory assays.

Root cause 3: Algorithms for test selection and use may not be sufficiently clear or prescriptive.

Root cause 4: Existing established governance processes for dealing with suspected test performance issues in a timely fashion may be underutilised.

Root cause 5: Clinicians may act on laboratory results in inappropriate ways.

Root cause 1

There is insufficient understanding of the regulatory framework relating to the quality and clinical utility of commercial serological assays.

CE marking may be regarded as a quality mark and give a false reassurance about the robustness and efficacy of clinical laboratory tests. The CE marking may be taken to imply safety and conformity to the manufacturer's intended purpose for the assay, and to assessed quality standards, but does not necessarily imply the highest standards of sensitivity or specificity for clinical laboratory diagnosis.

The regulatory framework for safeguarding 'the health of the public by ensuring that medical devices work and are acceptably safe' provides no power to require manufacturers of raw materials to divulge to the competent authority to which other manufacturers those materials have been supplied.

Recommendations

- there is insufficient understanding of the limitations of the CE marking process; what the CE mark stands for in terms of assay performance should be more widely known
- senior PHE personnel should arrange a meeting with MHRA to discuss issues around the regulatory framework and how they might be improved
- the importance of adequate verification of commercial assays when introduced into a laboratory should be further stressed; validation of commercial assays is often quite limited. Examination of evidence of appropriate verification of assays and of ongoing quality assurance should be a standard part of laboratory accreditation assessments
- PHE experts should compile a guidance note on validation and verification of serological assays (similar to that recently written for molecular assays). It should be published as a Standard for Microbiology Investigation on the PHE website

Root cause 2

There are deficiencies in quality assurance systems for certain laboratory assays:

- some assays may not have optimal verification due to lack of suitable samples
- some assays may not be adequately quality controlled when in use because of the absence of a national external quality assurance scheme, or because of the lack of material for regular internal quality assurance checking
- if assays regularly pass their run validation criteria and do not fail Westgard rules it may be difficult to recognise at an early stage an unexpectedly high false result rate
- a strengthening of the process for early identification of greater numbers of reactive results than expected is desirable

- samples referred to reference laboratories may have inadequate clinical information and limited information on the local test results that led to referral. This can make it more difficult to recognise results obtained by the reference laboratory that are inconsistent with the clinical presentation, potentially leading to delays in identifying a problem with a test

Recommendations

- approach the National External Quality Assessment Service (NEQAS) to request additional IgM testing within the existing treponemal IgM scheme where sample numbers allow
- a national serum bank should be set up to store samples from rare and relatively uncommon conditions, including samples representative of different stages of infection that can be made available for test validation, verification and ongoing quality assurance. For syphilis, this would allow the creation of a bank with useful numbers of samples from primary infection, where IgM testing is most useful
- PHE experts should compile a guidance note on validation and verification of serological assays (similar to that recently written for molecular assays). It should be published as a Standard for Microbiology Investigation on the PHE website
- exceedance criteria should be ascertained for all serological assays to allow early recognition of changes in pattern of results
- reporting of test results should, where staffing permits, be arranged so that there are periods of continuity in reporting by one individual for one test area, allowing easier recognition of trends in results
- laboratories should maintain regular dialogue with clinical colleagues to discuss changes in local patterns of infection such as syphilis, and should regularly refer to national epidemiological information resources to identify changes
- reference and referral laboratories should further encourage referring laboratories to include the results of the initial testing and the clinical information with the referred specimen

Root cause 3

Algorithms for test selection and use may not be sufficiently clear or prescriptive. This may lead to unintended consequences when laboratories provide a rapid service to reduce turnaround times for panels of tests to a minimum. For example, a test might be done simultaneously with other tests rather than as a reflex test following earlier test results. These unnecessary tests have the potential to lead to over-interpretation of individual reactive results.

Testing algorithms try to give guidance on acceptable standards of testing and confirmation. They can be difficult to frame when they attempt to cover what follows after differing approaches to screening, leading to lack of clarity. The treponemal testing algorithm V44 in use at the time of this incident is an example where the role of IgM testing at different stages of infection was not well defined.

Recommendations

- published algorithms and guidelines, including those from specialist societies and the Standards for Microbiology Investigations available on the PHE website, should be clear on the need for confirmation of tests and give clarity on appropriate testing models, particularly where appropriate tests may differ at different stages of an infection
- laboratory standard operating procedures should always include clear reporting criteria and comments compatible with the advice in published peer-reviewed national guidance

Root cause 4

Existing established governance processes for dealing with suspected test performance issues in a timely fashion may be underutilised.

- laboratory meetings do not always lead to documented actions with timelines for review, and may be restricted to small numbers of staff in reference laboratories
- clinical audits are undertaken by the laboratories, however, they may not provide the full picture about whether patient management is affected by test result interpretation
- although there is a process for alerting senior staff external to the laboratory or within the governance structure of PHE to a potential issue this could be further clarified and defined
- there is a lack of written guidance on further defined actions to take, for example, further testing and communication with other laboratories when suspected test performance issues arise
- concerns about the performance of an assay may not be raised promptly because of some uncertainty as to the validity of the concerns, especially in the face of manufacturer or distributor doubts of any problems. In addition, laboratory staff may be wary of reporting concerns over assay performance to MHRA until they have a substantial amount of data, delaying the process. This results from a misperception of the role of MHRA, which should be involved at an early stage so that a body of information can be gathered in one place to inform the scale of a

problem, the manufacturer can be contacted, and consideration given to an investigation

Recommendations

- meetings of laboratory staff should be held more regularly, preferably weekly, to allow discussions of possible problems
- enhance the procedure to ensure that concerns about assay performance are reported to senior staff at an early stage regardless of feedback from the test manufacturer. A suggested appropriate forum would be a regular laboratory quality meeting where external and internal quality assessment (EQA and IQA) and general test performance are reviewed
- for laboratories within which specialised services function to some extent independently, and where services are provided from more than one site, there is a need to have local quality meetings in each area and, in addition, frequent laboratory/centre-wide quality meetings, thus allowing a broader scrutiny of potential problems. Such meetings should always include medical staff so that potential risks to clinical patient management and public health are discussed in a wider forum and not underestimated
- clinical governance arrangements for reference laboratories should ensure that there is regular medical as well as scientific review at all stages of the testing pathway, with both medical and scientific input into defining the quality parameters within which complex serology is performed
- clear guidance as to when a deviation from the expected pattern of test results would trigger the involvement of expert medical and scientific assessment at an early stage
- reassurance from a kit manufacturer that an assay is performing satisfactorily outside the laboratory where concerns have been raised should not delay wider investigations and discussions with other laboratories using the test
- formal networks of interest groups among PHE laboratories should be established to provide regular exchange of information on particular topics in laboratory diagnosis, including areas such as syphilis, blood borne viruses and testing in the immunocompromised. The creation of such regular, formal meetings will facilitate ad hoc informal contact with colleagues at an early stage when problems are suspected
- MHRA should be informed at an early stage when an assay deficiency is suspected, in line with PHE policy

Root cause 5

Clinicians may act on laboratory results in ways that do not take account of caveats expressed in the interpretive comments associated with reported results due to insufficient dialogue between clinicians and laboratory personnel.

Recommendations

- increased opportunities for dialogue between laboratory and clinicians should be sought, including joint educational meetings
- further education and training in the area of interpretation of syphilis serology and its pitfalls should be available, especially for junior clinical staff
- national clinical management guidelines (such as ‘UK National Guidelines on the Management of Syphilis 2008’) should have strengthened sections on syphilis serology, including discussion about the possibility of false positive results as well as false negatives

Acknowledgements

Many individuals contributed to this investigation.

Sincere thanks to HPA colleagues, including the laboratory staff at STBRL and HPA Birmingham; health protection units and regional leads; the communications team; Anu Jain, microbiology registrar, for reissuing the reports, and Iain Kennedy, public health registrar, for co-ordinating the look-back debrief.

In the NHS, sincere thanks to all participating microbiologists, GPs and GU physicians; SHA directors and trust medical directors, and Jim Stephenson, from the microbiology department at St Helier Hospital, for review of the material.

Thanks to Stephen Lee of the MHRA.

In addition, much appreciation to the experts consulted for all aspects of work of the three Incident Teams.

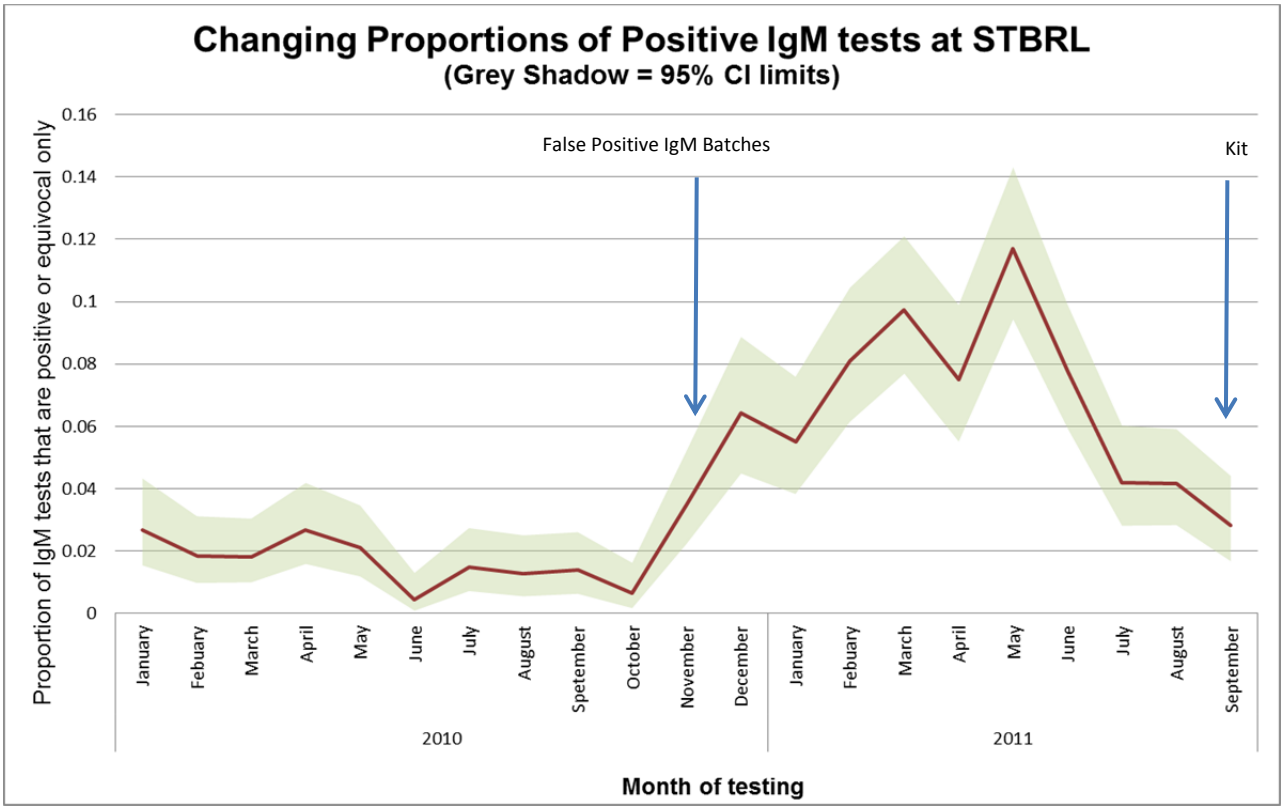
Appendix 1: Syphilis trends in England 2010-11

A) Diagnoses of Infectious Syphilis

B) Increase in IgM Test Positive Cases at STBRL

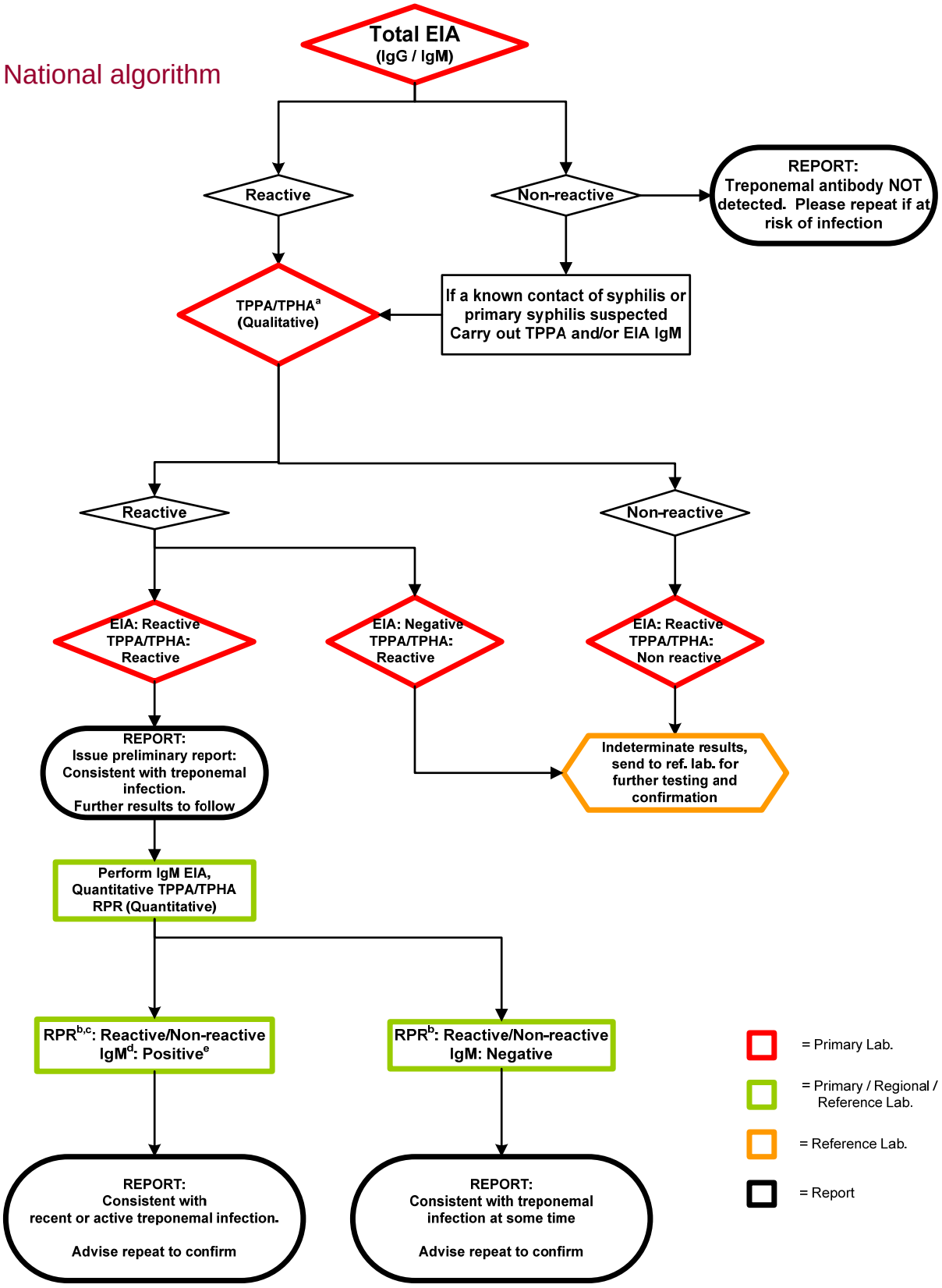
Month	Year	IgM Only	IgM Batch
January	2010	10	4491
February	2010	7	4491
March	2010	8	4491
April	2010	12	4491
May	2010	13	4991/050x1
June	2010	1	050x1
July	2010	7	050x1
August	2010	4	050x1/051x1
September	2010	7	051x1
October	2010	3	051x1
November	2010	15	052x1
December	2010	24	052x2/053x1
January	2011	25	053x1
February	2011	44	053x1
March	2011	51	053x1
April	2011	36	053x1
May	2011	67	053x1
June	2011	45	05411a
July	2011	23	05411a
August	2011	23	05411a
September	2011	14	05411a/Lab21

Appendix 2: Changing proportions of positive IgM tests at STBRL



Appendix 3: Serological diagnosis of syphilis

A) National algorithm



Footnotes to National Algorithm

a) Carry out a clot check. A clot check is done to make sure that there has not been an error in producing aliquots. It is a repeat test done not from the separated aliquot of serum which has already been tested and which has given the initially reactive result, but rather from the original tube of clotted blood which is likely to contain clot and some residual serum and which will have the original patient identifier label from the sender.

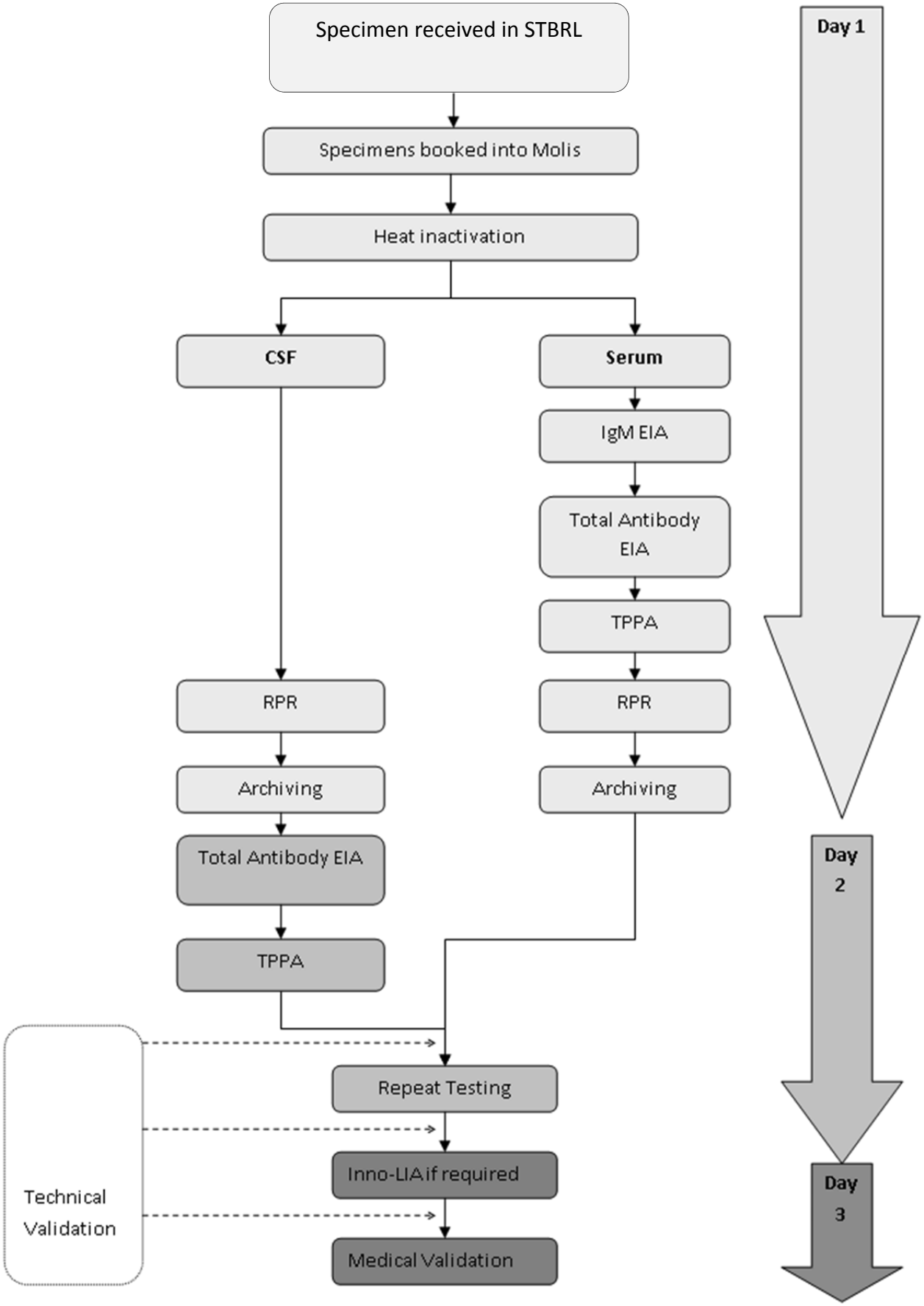
b) RPR titre is used in laboratories to help assess whether infection is likely to be recent or adequately treated; a persisting RPR titre of >16 is seldom seen in an adequately treated infection.

c) Failure of a fourfold fall in RPR titre by six months, and an eightfold fall by one year post-treatment raises concerns about treatment failure or reinfection. A significant rise in RPR titre or IgM level raises concern about reinfection. There may be a more gradual fall in RPR titre in those treated in the latent or late stages and in those who have had multiple episodes of syphilis; 50% of these become ‘serofast’ ie have low titres persisting for >2 years, not reflecting treatment failure1.

d) Treponemal IgM results must be interpreted with care. Positivity reflects active infection but can persist for 12-18 months after treatment of infection2.

e) Low IgM levels can indicate: persisting antibody from a previous infection: new infection: nonspecific infection. Low IgM positive will vary depending on the kit used but falls near to the cut-off. A repeat should be requested to detect a rise or fall in antibody level.

B) STBRL algorithm



Appendix 4: Syphilis serology

Overview of syphilis testing:

In England and Wales, less than 200 laboratories perform approximately 1.5 million tests per annum (900,000 sexual health and 600,000 antenatal screens). Seven regional PHE laboratories perform primary diagnostic and confirmatory testing on 200,000 of these samples. STBRL performs 10,000 tests per annum, approximately 85% of which are through its regional remit. Over 99% of these samples will have had at least one prior positive syphilis antibody test at a primary diagnostic test location. Increases in false positive IgM test results may have occurred in other laboratories using the same kit over the same period of time.

Syphilis diagnosis:

The screening algorithms for syphilis are complex and nuanced, as many laboratory tests are used to provide a composite picture of the likelihood of recently acquired, established, or treated disease. Both list IgM testing as part of a confirmatory strategy. National guidelines are a consensus of expert opinion on the role of IgM in the algorithm. There is, however, no universal standardisation, and the use of only one type of serologic test is insufficient for diagnosis, because each type of test has limitations, including the possibility of false-positive test results in persons without syphilis. Alternative tests used include rapid plasma reagin (RPR), *Treponema pallidum* particle agglutination assay (TPPA), and an enzyme immunoassay (EIA) detecting total treponemal antibodies (EIA Total.) Discrepancies exist in interpretation, with any detectable RPR titre used for correlation with disease activity in the USA, but not in the UK, where a RPR titre of >1:16 is afforded clinical significance as an indicator of active infection.

UK and local trends:

There was little increase in overall syphilis diagnosis during the period from January 2010 to June 2011. Conversely, in STBRL testing there was a near doubling in IgM positive tests from 930 (September 2009 to August 2010) to 1,673 (September 2010 to August 2011), with no associated increase in overall testing (9,804 versus 9,137). Numbers of samples with IgM positive and other tests negative more than trebled from 94 to 356, and those with an additional weakly positive RPR (<=1:16 dilution) doubled (191 versus 403).

Appendix 5: Incident control team Terms of Reference and team composition

A) Overall Incident Group Terms of Reference

1. The team will be led by a Senior Responsible Officer (SRO) for project management of implementation of remedial actions within the HPA, including those relating to clinical governance.

2. Co-ordinate for HPA incident response following identification of false positive syphilis diagnosis.

3. Evaluate scale and duration of problem within HPA, identify required remedial actions.

4. Ensure communication and liaison with NHS, MHRA, and other relevant stakeholders, internal and external.

5. Provide regular reports and briefing to MS and HPS SMT, CEO and Board as required.

6. Work with senior HPS colleagues to identify public health action required arising from this incident, and as appropriate, provide input into any look-back exercise led by public health colleagues.

7. Advise the Executive Director about necessity for investigation into working arrangements and clinical support to STBRL.

Membership:

Ken Mutton (Chair)	Clinical Virologist, Manchester
Ian Sharp	Head of Quality at HPA Colindale
Colin Brown	ID Academic Clinical Fellow, HPA Colindale
Gwenda Hughes	STI Section Head, STI Surveillance, HPA Colindale
Emma Gilgunn-Jones	Chief Press Officer, HPA Colindale
Paul Crook	Regional Epidemiologist, HPA Victoria
Erasmus Smit	Consultant Microbiologist, Birmingham
Margaret Logan	Deputy Regional Microbiologist, Birmingham
Cathy Ison	Director of STBRL, HPA Colindale
Gavin Dabrera	Public Health Registrar, seconded to HPA Colindale
Maria Zambon	Director of Reference services, HPA Colindale
Patrick French	GUM Consultant, Mortimer Market, London
Margaret Kingston	GUM Consultant, Manchester
Ash Sukthankar	GUM Consultant, Manchester

B) Look-back Group Terms of Reference

1. Review the details of the incident to determine the possible adverse impact on patients;
2. Based on this review, make an early decision regarding the need
   - to re-test samples
   - to contact patients including whether to re-test patients
3. If a decision is made to re-test samples, agree the scope and nature of the re-testing required;
4. If a decision is made to contact patients, agree the scope and the nature of this contact, including any re-testing required;
5. Co-ordinate and oversee the undertaking of the process of patient contact including relative communication handling;
6. Prepare a report for the Executive Group summarising the decisions taken and the process followed and outcome of any re-testing or patient notification exercise;
7. Consider the need for any further evaluative work.

This group did not review any other implications for microbiology services of this incident.

Membership:

As with ICT (Chair, Paul Crook)	
Ian Sharp	Head of Quality at HPA Colindale
Rachel Heathcock	Director, SEL HPU
William Tong	Consultant Virologist, St Thomas' Hospital
Robin Smith	Consultant Microbiologist, Royal Free Hospital
Kirstine Eastick	Director, Scottish Bacterial STI RL
Simon Cathcart	CCDC, NEL & NCL HPU
Lesley Wallace	Epidemiologist, HP Scotland

C) Laboratory Review Group Terms of Reference

1. Review details of laboratory testing protocols

a. Including national and local SOPs, algorithms, interpretive comments

2. Review details of laboratory quality systems including review of:

a. Validation and verification of assays

b. EQA performance

c. IQC performance

d. IQA performance

e. Quality policy/meetings etc

f. Nonconformity management

3. Consider areas for further investigation

a. Including corporate management

4. Prepare report for ICT and EG

a. Including root cause analysis

Membership:

Ken Mutton	Clinical Virologist, Manchester
John Parry	Deputy Director, VRD, HPA Colindale
Andrew Turner	Interim Head, Public Health Laboratory Manchester.
Ian Sharp	MS Head of Quality

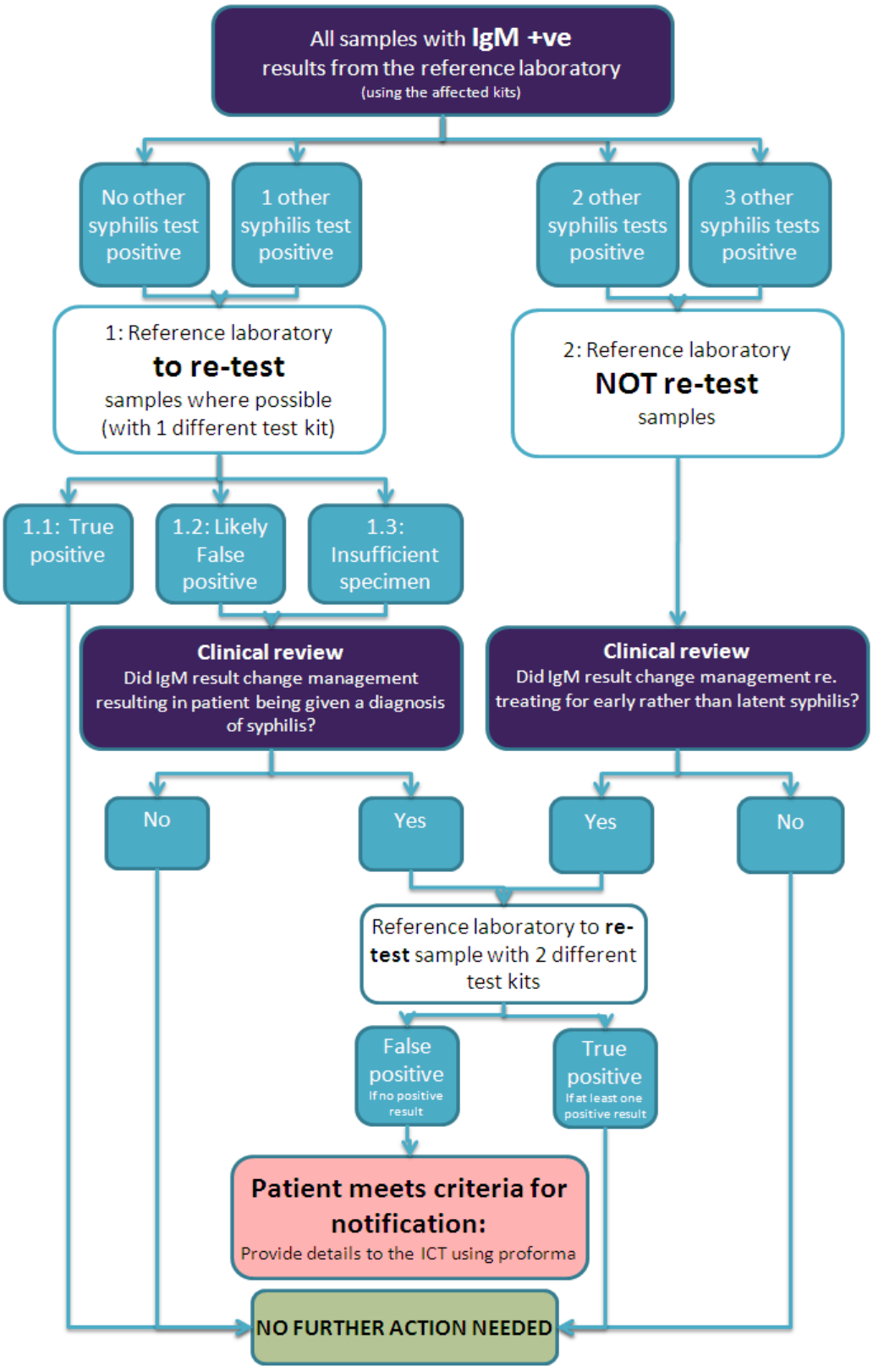
Appendix 6: Timeline

Date	Event
13 Jun 2011	HPA written alert to Mercia, re concerns over test
24 Aug 2011	Mercia release Product Safety Notice (supplementary notice 28 Oct 2011)
11 Oct 2011	1st CEO briefing
12 Oct 2011	Discussed with NEQAS
12 Oct 2011	Level 3 incident declared
14 Oct 2011	HPA reported Medical Device Adverse incident to MHRA
14 Oct 2011	1st Incident Control Team (ICT) (MS led)
24 Oct 2011	HPA Briefing Note
25 Oct 2011	2nd ICT, (MS led)
31 Oct 2011	Re-testing commenced at reference laboratory
03 Nov 2011	Medical Device Alert issued by MHRA
15 Nov 2011	1st Look-back group meeting (HPS-led)
15 Nov 2011	3rd ICT (MS led)
18 Nov 2011	All laboratories using the kit identified
02 Dec 2011	4th ICT (MS led)
02 Dec 2011	2nd Look-back group meeting (HPS led)
12 Dec 2011	3rd Look-back group meeting (HPS led)
21 Dec 2011	4th Look-back group meeting (HPS led)
06 Jan 2012	STBRL Laboratory review
12 Jan 2012	5th Look-back group meeting (HPS led)
31 Jan 2012	6th Look-back group meeting (HPS led)
13 Feb 2012	7th Look-back group meeting (HPS led)
20 Feb 2012	8th Look-back group meeting (HPS led)
27 Feb 2012	HPA Birmingham Laboratory review
02 Mar 2012	9th Look-back group meeting (HPS led)
06 Mar 2012	10th Look-back group meeting (HPS led)
09 Mar 2012	11th Look-back group meeting (HPS led)
19 Mar 2012	12th Look-back group meeting (HPS led)
05 Apr 2012	13th Look-back group meeting (HPS led)
02 May 2012	14th Look-back group meeting (HPS led)
24 May 2012	5th ICT (MS Led)
14 Jun 2012	Incident Debrief
27 Sep 2012	STBRL Laboratory Briefing

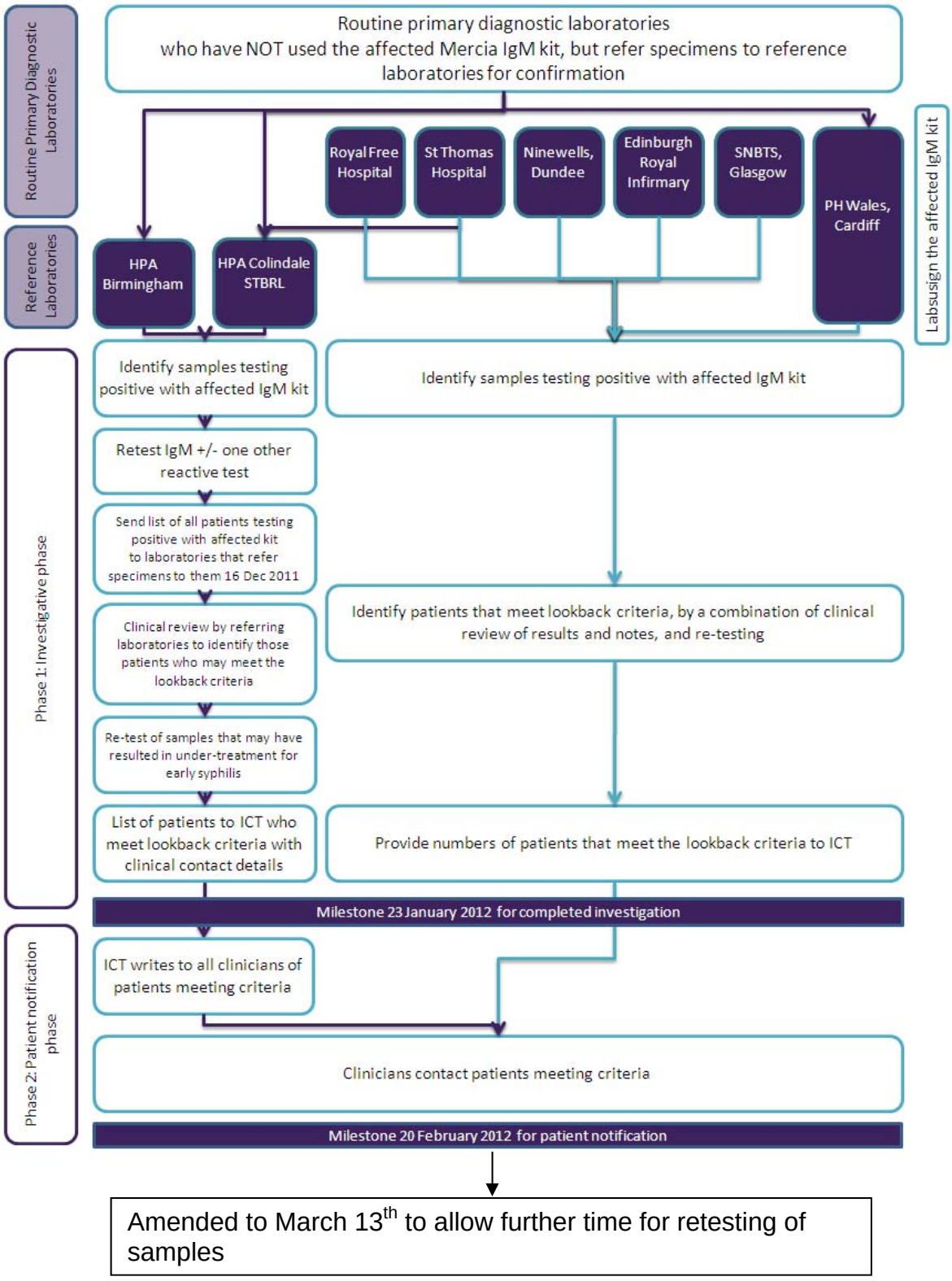
Timetable	
Phase One	**Investigation phase**
16 Dec 2011	HPA reference laboratories wrote to microbiologists at laboratories that refer specimens to them, with a list of patients affected. These hospitals will need to clinically review the notes and results of these cases to identify those that may meet the look-back criteria
23 Jan 2012	Deadline for completion of investigations for laboratories referring specimens to HPA Colindale STBRL and HPA Birmingham, and deadline for investigations in the other 6 laboratories who have used the affected kit
Phase Two	**Patient notification phase**
23 Feb 2012	All samples retested at STBRL or local hospital
13 Mar 2012	Treating clinicians to contact patients meeting the look-back criteria
Phase Three	**Outstanding patients**
May 2012	Final investigations to be completed by all hospitals
Jun 2012	Treating clinicians to contact patients meeting the look-back criteria
Jul 2012	All extra samples to be retested at STBRL

Appendix 7: Co-ordinated testing approach

A) Re-test algorithm



A) Re-test flow-chart



Amended to March 13th to allow further time for retesting of samples

Appendix 8: Example of information sheet provided to laboratories

Patients that require clinical review if IgM changed management													
Patient Information						Original results					Management		
HPA NUMBER	HOSPITAL	RECEIPT DATE	LAB REF NO	PII	DOB	TOTAL EIA RESULTS	TPPA	RPR	INNO-LIA	MERCIA IgM EIA	IGM CHANGED MANAGEMENT?	CHANGED MANAGEMENT HOW?	ANY OTHER COMMENTS
HPA0123456	A&E	07/07/11	12345678	ABCD1234	17/05/79	Negative	Negative	Negative	Not required	Positive			

Appendix 9: Communications materials

A) Guidance for microbiologists on dealing with the retest results

B) Guidance for clinicians on contacting affected patients

C) Syphilis testing factsheet for affected patients

D) Q&As for clinicians

E) MISDIAGNOSIS template letter for local adaptation

F) UNDERTREATMENT template letter for local adaptation

G) INSUFFICIENT sample template letter for local adaptation

A) Guidance for microbiologists on dealing with the retest results

We would like to restate our sincere thanks for all of the time and effort that you have put into this look-back exercise. We have sent you the results of retesting and this document provides guidance on the steps needed to assess whether a patient needs contacting and with recommendations on how to contact patients.

The Incident Control Team (ICT) will be contacting you by telephone to ensure that the process is clear and will liaise where possible with identified clinicians.

There are two main steps in the process.

Local assessment of whether a patient needs contacting
Contacting the patient

ICT recommendations on which patients need contacting
The ICT has recommended that patients meeting the criteria in Table 1 should be contacted as they may have been adversely affected by an incorrect syphilis IgM result.

Patients whose management has not been affected by a false positive result do NOT meet the criteria and do NOT need to be contacted.

Table 1: Criteria for identifying patients that need contacting. Patients must meet ALL 3 criteria

1	They have a likely false positive IgM result	Defined as a reactive Mercia IgM kit result with the affected batch numbers AND EITHER where the specimen has been retested indicating the original result was probably due to non-specific cross-reactivity OR there was insufficient sample to retest.
2	They were given a diagnosis of syphilis	
3	The IgM result changed their clinical management in one of three ways	They were given a diagnosis of syphilis and/or offered and/or received treatment OR They were treated for an earlier stage of syphilis than if the IgM result was negative, resulting in under-treatment i.e. receiving a shorter course of treatment OR They were unnecessarily retreated, if they had existing markers of syphilis.

Local assessment of whether a patient needs contacting
The ICT's role is to provide advice and support. Whilst the ICT has made recommendations on which groups of patients need contacting, this guidance cannot replace clinical decision-making. The decision to contact individual patients is therefore a local one.

Local clinicians, microbiologists and GUM colleagues are asked to work together to review all the retesting results and the clinical management of the patient and then decide:

a) Whether contacting the patient is appropriate

b) The reason for contacting the patient e.g. because they may have been misdiagnosed, under-treated or where there is insufficient sample
c) On the further follow-up and clinical management of the patient

It is anticipated that for some patients the results from re-testing may remain indeterminate. These will need careful clinical review.

Retesting results
You have previously sent the ICT information on patients where it is possible that the syphilis IgM result changed their management. We have now retested samples from these patients, using a battery of tests.

The results of retesting are attached in a spreadsheet. Please note that these will also be available on your LIMS system and the full interpretative comment will only be available on this system. We advise you to review these full reports.

Please also note that the spreadsheet contains the results of testing of multiple samples from the same patient.

Please contact Sexually Transmitted Bacteria Reference Laboratory (STBRL) if you require further support with the interpretation of the results.

The overall results of retesting
The overall results of retesting for patients originally testing positive or equivocal using the affected batches of Mercia (Microgen Bioproducts) Syphilis M kit are:

- For patients who only had IgM reactivity or those who had IgM and one other test reactivity (out of four syphilis tests), the degree of false positivity with the Mercia Syphilis M kit on retesting with two different kits was found to be approximately 95%.
- For patients with multiple test reactivity (out of four syphilis tests), the degree of false positivity with the Mercia Syphilis M kit on retesting with two different kits was approximately 75%.

Contacting patients
It is important that patients are contacted in a confidential and sensitive manner. Please read the communication guidance attached and send it to the clinicians of the affected patients.

Please note that this has been significantly revised since it was circulated previously and so discard previous guidance.

We would be very grateful if you can let us know the outcomes of your patient notification, particularly how many patients were assessed as requiring contact, the reason for contacting them and whether their follow-up has been completed. These fields are contained on the attached spreadsheet.

Attachments
- Results of retesting
- Communication guidance
- Clinician Q&As

- Template letters if needed (this is suggested wording which can be edited for local use. It should only be used if telephone contact fails, and if written communication has been agreed with the patient)
- Patient factsheet if needed

Contact details
Please do not hesitate to contact us between 9.30am and 5pm, Monday and Friday on 020 8327 7563 or 020 8327 6166 (Colin Brown and Gavin Dabrera) or on syphilis-IgM@hpa.org.uk. Please note that these contact details are not for patient use.

Many thanks for your continued help in dealing with this problem.

The Syphilis Incident Control Team.

B) Guidance for clinicians on contacting affected patients

This document provides guidance for clinicians about the patient notification exercise. This is in relation to the likely false positives resulting from the use of the Mercia IgM syphilis kit. Please do not hesitate to contact the incident team at any point for help.

It is suggested that each clinical service nominates a lead to co-ordinate this for their patients. If this lead is not based in GUM services, they should make prior contact with their local GUM clinic so that patients needing further treatment, seeking further testing or sexual health advice, can be referred appropriately.

We recommend that the person contacting the patient is adequately briefed regarding the nature of the incident and the individual clinical detail. We have included Q&As for clinicians with supporting information.

ICT recommendations on which patients need contacting
The ICT has recommended that patients meeting the criteria in Table 1 should be contacted as they may have been adversely affected by an incorrect syphilis IgM result.

Patients whose management has not been affected by a false positive result do NOT meet the criteria and do NOT need to be contacted.

Table 1: Criteria for identifying patients that need contacting. Patients must meet ALL 3 criteria		
1	They have a likely false positive IgM result	Defined as a reactive Mercia IgM kit result with the affected batch numbers AND EITHER where the specimen has been retested and has been found to give results indicating the original result was probably due to non-specific cross-reactivity OR there was insufficient sample to retest.
2	They were given a diagnosis of syphilis	
3	The IgM result changed their clinical management in one of three ways	They were given a diagnosis of syphilis and/or offered and/or received treatment OR They were treated for an earlier stage of syphilis than if the IgM result was negative, resulting in under-treatment i.e. receiving a shorter course of treatment OR They were unnecessarily retreated, if they had existing markers of syphilis.

Local assessment of whether a patient needs contacting
The ICT's role is to provide advice and support. Whilst the ICT has made recommendations on which groups of patients need contacting, this guidance cannot replace local clinical decision-making. The decision to contact individual patients is therefore a local one.

Local clinicians, microbiologists and GUM colleagues are asked to work together to review all the retesting results and the clinical management of the patient and then decide:-

d) Whether contacting the patient is appropriate
e) The reason for contacting the patient e.g. because they may have been misdiagnosed, under-treated or where there is insufficient sample
f) On the further follow-up and clinical management of the patient

It is anticipated that for some patients the results from re-testing may remain indeterminate. These will need careful clinical review.

How should I contact patients?
All communication should be conducted in a confidential and sensitive manner.

Clinicians who do not consider themselves specialists in sexual health will retain responsibility for contacting any affected patients but may wish to seek advice from local GUM and microbiology consultants.

The incident team recommends that clinicians should contact patients only by the methods of communication the patient has previously agreed to, e.g. some GUM patients may have previously stipulated that they do not wish to be contacted by letter.

Unless previously requested otherwise by the patient, the incident team recommends that initial contact is made by telephone.

Every patient should have the opportunity to discuss their results with an experienced sexual health clinician in person if they wish and therefore they should be offered an appointment.

Clinicians may use the appropriate letter and clinicians' Q&A to help prepare for such a phone call or appointment. If a patient requests such an appointment, please arrange a scheduled appointment within the week, rather than a walk-in clinic.

If it is not possible to contact the patient by telephone within a week, then we have provided a template letter that can be used to contact the patient if appropriate to do so. There are different letters for different scenarios e.g. one for a misdiagnosis, one for those undertreated and one for those where there was insufficient sample. Please take time to ensure that you use the right letter and adapt it to meet the individual patient circumstances.

The letters should be marked private and confidential and edited to include any relevant patient specific information, contact details of your local lead and the letters should be printed on your organisation's headed paper.

If you choose to write to the patient, please ensure that letters are posted to avoid arriving on Fridays or Saturdays when patients may find it difficult to access healthcare services, e.g. send letters on a Monday.
We understand that some clinicians may wish to give all this information only during an appointment. Please use the information in the clinicians' Q&A document and the template letters, to prepare for this.

When should I make contact?
Look-back exercises are most effective when patient notification is co-ordinated across all affected organisations.

We therefore request that first contact with patients should start from the 13 March 2012. However, clinical need overrides any concern for a co-ordinated approach (eg antenatal patients prior to delivery).

Supporting documentation
The following documents are available from the incident team:

Letter 1 – for those who may have been misdiagnosed as having a syphilis infection (either first infection or reinfection)
Letter 2 – for those who may have been undertreated because of the IgM result
Letter 3 – for those tested with an affected kit but need re-bleeding to enable re-testing as there were insufficient samples.

Clinician Q&As – these are answers to commonly asked questions which clinicians can use to understand the issues relating to this incident. This should not be given to patients.

Patients' factsheet – this is a brief explanation of issues for patients. This can be sent to patients if they request more information, but not automatically.

Media Communications
The national lead for communications (such as press enquiries) is the Health Protection Agency. Assistance for dealing with media enquiries can be directed to the HPA communications division.

Follow up
We would be grateful if you could let us know which patients you have identified that need contacted, the reason for this and when follow-up is complete. This information can be fed back to the incident team via your local microbiologist who will be able to complete a spreadsheet and return this.

Thank you
We understand the pressures that this investigation has placed in clinical teams and we are very grateful for your help. Responding to the possible adverse effects of the faulty batches of this kit has required an intense effort from all those involved.

Enquiries
Please direct enquiries from clinicians relating to operational matters to the Incident Team via syphilis-IgM@hpa.org.uk. The incident team can also be contacted between 9.30am and 5pm between Monday and Friday on 020 8327 7563 or 020 8327 6166 (Colin Brown and Gavin Dabrera). These contact details are not for patient use.

C) Syphilis testing factsheet for affected patients

Key points

- Syphilis is an infection which can be spread through unprotected oral, anal or vaginal sex. It can also spread from pregnant women to their unborn babies.
- It causes various symptoms depending on the stage of development of this infection. The infection starts with an ulcer on the genitals, often followed by rashes.
- You can reduce your risk of syphilis infection by using condoms during sexual intercourse.
- Several laboratory tests are used to diagnose syphilis infection from blood samples.
- One of these, a commercially available laboratory test for syphilis has produced a high level of incorrect results.
- This occurred for patients tested between November 2010 and September 2011.
- As a result of this a small number of patients may have been given a wrong diagnosis of syphilis. These patients did not actually have a new syphilis infection and received unnecessary treatment. Although the treatment would not have any long lasting effects on health, a diagnosis of syphilis may have adversely affected them. They will be contacted by their doctor, but no further testing or treatment is needed.
- Other patients may have been correctly diagnosed as having syphilis. However, the stage of their infection may have been incorrectly diagnosed as early stage syphilis when it should have been late stage syphilis. Whilst these patients would have received a course of antibiotics, they would not have received the standard course of treatment for the later stage. These patients will be contacted to arrange further antibiotic treatment.
- All the affected patients represent only a very small proportion of all those who are tested each year for syphilis.
- Patients who were told they were NOT infected with syphilis are unaffected by this. They can be reassured that they have the correct results.
- Patients who have not been contacted by their doctor about this need take no further action.

Questions and Answers

Why has this happened?

A problem has been identified with three batches of a commercial test kit used in laboratory testing for syphilis which gave incorrect results. The affected kits produced high levels of incorrect results for a particular type of antibody used to diagnose syphilis. This means that the test was positive even though the patient did not have the antibody. This test was only one of several tests which were used in combination for syphilis. This means only a small proportion of people who had syphilis testing will be affected by this problem.

What has been done to stop this problem?

The affected tests have been withdrawn by the manufacturer and affected laboratories have stopped using them. The Medicines and Healthcare products Regulatory Agency (MHRA), which regulates this type of equipment, has issued a national Medical Device Alert. This will warn any laboratories in the United Kingdom from using the affected tests.

How do I know if I have been affected by this? What should I do?

Results have been checked for syphilis tests in the UK for the period when the unsatisfactory test kits were used. Anyone who received the wrong diagnosis or has had their treatment affected, will be contacted by the doctor or clinic that did the testing. If you have not been contacted by your clinic, you can be reassured that you are not affected.

People who were incorrectly diagnosed with syphilis will have been prescribed antibiotics, which would not have had lasting effects on their health. They will be contacted by their doctor to discuss this but no further testing or treatment is necessary.

Some people who have been incorrectly diagnosed as early stage syphilis rather than late stage syphilis will need a longer course of antibiotics. They will be contacted by their doctor to arrange this.

Can syphilis testing be trusted?

This type of problem only occurs very occasionally. Most patients have been given the correct diagnosis as more than one type of test had been used. It is still very important to be tested for sexually transmitted infections such as syphilis, as these often do not have symptoms. Sexual health clinics have specially trained staff and the correct equipment to test for syphilis and other sexually transmitted infections (STIs).

What is syphilis and how do people get it?

Syphilis is an infection caused by a bacterium called *Treponema pallidum*. It is mainly spread through unprotected oral, anal or vaginal sex (ie without a condom). It can also be passed from an infected pregnant woman to her foetus, through the placenta and during childbirth.

How common is syphilis?

It is less common than other sexually transmitted infections. In England, there were 1,858 cases of infectious syphilis reported in 2010. Most of these cases were in men rather than women. Rates of syphilis in England have been stable over the past five years.

How do I know if I have syphilis?

The symptoms of syphilis will vary depending on what stage of development, the infection is at. In the early stage, there can be an ulcer on the genitals. Rash can develop after this. In the late

stages, if there is no treatment, problems can slowly develop related to the brain or circulation. Some people might not realise they have symptoms, so it is important to be tested in a sexual health clinic, if you have had unprotected sex.

Can syphilis be cured?
Yes, syphilis infection can be treated with antibiotics. Once an appropriate course of antibiotics has been given, the infection can no longer be spread to others, symptoms will be relieved and the disease will not progress.

How can I protect myself against syphilis infection?
Using a condom when having sex, and reducing the number of sexual partners you have are the best ways to protect against infection. If you are a pregnant woman, you will be offered a blood test for syphilis infection in the antenatal clinic. If necessary, antibiotics can prevent the infection spreading to your unborn child.

I'm worried I have syphilis – How can I find out if I do?
Blood tests for syphilis can be performed by your general practitioner or your local sexual health clinic. Specialist tests can also be performed on any genital ulcers you may have, at your local sexual health clinic. Unprotected sex increases your risk of all sexually transmitted infections, not just syphilis. Therefore you may be offered tests for these at the same time. The doctor or nurse who sees you will be able to advise you.

You can find your local sexual health clinic on the NHS Choices website. Sexual health clinics keep all your information confidential.
www.nhs.uk/ServiceDirectories/Pages/ServiceSearchAdditional.aspx?ServiceType=SexualHealthService

D) Q&As for clinicians

Key messages

- Three batches of a commercially available lab test for treponemal IgM, distributed between November 2010 and September 2011 have produced high levels of false positive results. The MHRA has issued a medical device alert in November 2011 to alert laboratories to stop using the affected kits.
- The issue with the kits was false positive results, rather than false negatives and as a result there is no issue of missing a syphilis diagnosis or any immediate public health risk from undiagnosed syphilis.
- Diagnosing syphilis is complex and involves a number of blood tests and consideration of the clinical presentation. Therefore, in the vast majority of cases, a single incorrect IgM result, would not have impacted on patient management.
- However, some individuals may have been given an incorrect diagnosis of syphilis (either a first episode or a re-infection). Those prescribed with antibiotic treatment for false positives will suffer no lasting impact on their health. However, an incorrect diagnosis of syphilis may have adversely impacted upon them in other ways, including their relationships.
- In a small number of cases, patients correctly diagnosed with syphilis may have been regarded as being at an earlier stage of infection than was actually the case. This could

have led to some patients not receiving sufficient treatment to prevent complications of syphilis and these patients may require additional antibiotics.
- The HPA has led an investigation into the impact of the affected test kits and sought support from the local clinicians and microbiologists that were affected. This has included retesting of samples with different syphilis IgM kits.
- Those patients who have been given an incorrect diagnosis of syphilis or have been under-treated for syphilis will need to be notified by their clinician.
- Those people who received a negative test result have not been affected by this incident.
- Our advice: syphilis can only be caught via sexual contact – unprotected vaginal, oral or anal intercourse, or genital contact with an infected partner. Consistent condom use can help to reduce the risk of syphilis infection. Sexually active people can also reduce their risk of infection by reducing their number of sexual partners. Anyone concerned with their sexual health should speak to their sexual health clinician or other relevant health practitioner for advice. The NHS also has a great website: www.nhs.uk/Conditions/Syphilis/Pages/Introduction.aspx or visit the British Association for Sexual Health and HIV website for your nearest clinic: www.bashh.org
- Any persons affected by this will be contacted by their clinician. There is no need for individual patients to take any action unless they are contacted by their clinician.

Questions & Answers

Why have there been false positives?
A problem with three batches of a commercial Syphilis IgM testing kit has resulted in higher levels of false positive IgM results. These kits were used in eight laboratories across the UK.

As four blood tests are involved in making the diagnosis and clinical symptoms are also considered with this, only in a small proportion of cases have people been given the incorrect result or treatment – in the great majority of cases the right result has been given.

Are there any more of these kits still being used?
A Medical Device Alert was issued by the Medicines and Healthcare products Regulatory Agency (MHRA) in November 2011. This alerted laboratories to stop using the affected batches.

Who are affected by the incorrect results?
The majority of people whose samples were tested with this kit have not been affected. Anyone who has been affected will be informed.

The incident team has worked with clinicians and microbiologists to identify which patients' management was affected by an incorrect result. This was achieved through a combination of retesting using different test kits and clinical review of patient notes.

And what should those affected do?
Only those patients identified by the incident team in conjunction with their clinicians should be notified and the incorrect diagnosis discussed. Some patients will require a repeat serology and some patients will require further antibiotics.

How many people does the agency think has been affected?
We estimate that fewer than 100 people would have been adversely affected by this. This represents only a very small proportion of the total number of tests for syphilis performed

nationally each year. No false negative results, where the patient has a negative test result but actually has the infection, have been seen. Therefore there is no public health risk of onward transmission of undiagnosed or untreated disease. The affected tests have only been in use since November 2010 so anyone tested for syphilis before then will not have been affected by this problem.

What about the wider community? How will they be affected?
There should be no impact on the wider community. There is no need for anyone diagnosed with syphilis between November 2010 and September 2011, and who is not contacted as part of this look-back exercise, to be concerned about their result.

As no issues have been identified with people receiving a negative test when they actually had the infection, there is no public health risk of onward transmission or undiagnosed or untreated diseases as a result of this incident.

Can syphilis testing in the UK be trusted?
Yes. In the vast majority of cases the correct diagnosis was made as the IgM test is only one of a battery of four laboratory tests used to diagnose syphilis and these are diagnosed alongside clinical symptoms and risk factors. In any case only a minority of laboratories in the UK used the affected IgM test kits.

The HPA has strong quality control systems in place to ensure the accuracy of the tests that it uses and these systems helped identify the problem but very occasionally a problem with a batch of kit will lead to an incident like this.

It is important that people still continue to be screened for sexually transmitted infections and diseases if they believe they have been at risk as many STIs including syphilis are often asymptomatic and are only detected when individuals are screened for infection by laboratory tests.

What is the HPA doing?
The HPA alerted the manufacturer of the affected kits, and the manufacturer subsequently issued a product safety notice for three batches of their kits. The Medicines and Healthcare products Regulatory Agency (MHRA) was also informed. The HPA will continue to liaise with both of these organisations as required and is leading an incident control team (ICT) which is investigating the impact of the affected tests and has been co-ordinating the identification and notification of possibly affected individuals.

What is the MHRA doing?
MHRA issued a Medical Device Alert in November 2011 to ensure no other laboratory in the country continued to use the affected batches of the IgM test kit.
What if patients want to complain?
Please be aware of the normal complaints procedure for the Trust.

Who do I ask for more support?
For those patients who have been identified as being affected by this, it is important that the patient’s management is discussed with the GUM consultant and the microbiologist. If there are any operational queries please contact the incident team on syphilis-IgM@hpa.org.uk or by telephone (Colin Brown or Gavin Dabrera on 02083277563 or 02083276166.

E) MISDIAGNOSIS template letter

Text in [ ] should be entered by local clinic

PRIVATE and CONFIDENTIAL

To [patient name]

Dear [patient name],

Re: An issue with your recent syphilis test result

I am writing to you as you attended [name of clinic] at [name of hospital] in [month and year]. During your visit, you had a blood sample taken to test for possible syphilis infection. The process of accurately diagnosing syphilis is complicated involving a number of different tests.

We have recently been informed that a problem has been identified with one of the tests used for laboratory testing for syphilis during the period you attended [name of clinic]. This problem has led to a number of incorrect results, which suggested the possibility of syphilis in people who were not in fact infected.

We have checked your records and retested the blood samples you provided to us. As a result we believe that the diagnosis you were given was incorrect and that you did not have evidence of a syphilis infection when you were tested on [date].

Please accept my sincere apologies for the distress that has been caused by you receiving the incorrect diagnosis. The routine antibiotic treatment you received from the clinic is unlikely to have any impact on your health.

We would like to discuss this with you in more detail and to answer any further questions about your results ; please arrange an appointment with [me/ my colleague –state name] via [telephone number] between [available times].

Action has been taken relating to the test responsible for this problem. It has been withdrawn by the manufacturer and the Medicines and Healthcare products Regulatory Agency (MHRA) which regulates laboratory test kits has been informed and has acted on this information.

The Health Protection Agency, which runs England's reference laboratory for testing syphilis, has been working closely with doctors to identify people affected by this problem to ensure that they receive the correct results.

I would like to reassure you that any other results you have received while attending our service, are correct and are unaffected by this problem. I wish to apologise again for the concern that this will have caused you.

Yours sincerely,
[Clinic doctor]

F) UNDERTREATMENT template letter

Text in [ ] should be entered by local clinic

PRIVATE and CONFIDENTIAL

Dear [patient name],

Re: An issue with your recent syphilis test result

I am writing to you as you attended [name of clinic] at [name of hospital] in [month and year]. During your visit, you had a blood sample taken for possible syphilis infection. The process of accurately diagnosing syphilis is complicated involving a number of different laboratory tests.

We have recently been informed that a problem has been identified with one of the tests used for laboratory testing for syphilis during the period you attended [name of clinic]. This problem has led to a number of incorrect results. In some individuals, this underestimated the length of time for which they had been infected.

We have therefore checked your records and retested the blood sample you provided to us. We have confirmed that you did have evidence of a syphilis infection when you were tested on [date]. However, the results of retesting suggest that your infection may have been present for longer than the initial test result led us to believe.

This means that we may need to give you more antibiotics than we already have so that we can completely clear the infection and prevent any risk of complications. Please be reassured that you would not have been at risk of passing the infection on to anyone else since you were first treated.

Please accept my sincere apologies for any concern and inconvenience that may have been caused to you. As we need to arrange further antibiotic treatment we recommend that you arrange an appointment as soon as possible, by contacting [me/ my colleague –state name] via [telephone number] between [available times]. We will also be able to answer any further questions you have about your results, during your appointment.

Action has been taken relating to the test responsible for this problem. It has been withdrawn by the manufacturer and the Medicines and Healthcare products Regulatory Agency (MHRA) which regulates laboratory test kits, has been informed and has acted on this information.

The Health Protection Agency, which runs reference laboratory testing for syphilis in England, has been working closely with doctors to identify affected patients, to ensure that they receive the correct results and appropriate antibiotic treatment.

I would like to reassure you that any other results you have received while attending our service are correct and are unaffected by this problem. Once again, please accept my sincere apologies for any distress and inconvenience this issue will have caused you.

Yours sincerely,

[Clinic doctor]

G) INSUFFICIENT template letter

Text in [ ] should be entered by local clinic

PRIVATE and CONFIDENTIAL

Dear [patient name],

Re: An issue with your recent syphilis test result

I am writing to you as you attended [name of clinic] at [name of hospital] in [month and year]. During your visit, you had a blood sample taken to test for possible syphilis infection. The process of accurately diagnosing syphilis is complicated involving a number of different tests.

We have recently been informed that a problem has been identified with one of the tests used for laboratory testing for syphilis during the period you attended [name of clinic]. This problem has led to a number of incorrect results which suggested the possibility of syphilis in individuals who did not have this infection. Where this has happened we have been testing blood samples again with a more accurate test.

As you tested positive for syphilis, we would like to repeat your blood test using a different test. This way we can we can be sure you get the correct diagnosis. We have checked your records but we do not have any of your blood samples available to re-test. We would therefore like to arrange an appointment for these samples to be taken.

Please accept my sincere apologies for the inconvenience that has been caused by this issue.

Please do contact [me/ my colleague –state name] via [telephone number] between [available times], to arrange an appointment.

Action has been taken relating to the test responsible for this problem. It has been withdrawn by the manufacturer and the Medicines and Healthcare products Regulatory Agency (MHRA) which regulates laboratory test kits has been informed and has acted on this information.

The Health Protection Agency, which runs England's reference laboratory for testing syphilis, has been working closely with doctors to identify people affected by this problem to ensure they receive the correct results.

I would like to reassure you that any other results you have received while attending our service, are correct and are unaffected by this problem.

I wish to apologise again for the concern that this will have caused you.

Yours sincerely,

[Clinic doctor]

Appendix 10: Hospital communication forms

A) Contact sheet log

HPA person initials	Date of call	Time of call	Who calling	Contact Details	Caller status	Discussion/advice given	Further follow up needed
CSB	20/03/2012	11:57:00	Example Micro	01234 5678910	Microbiologist	Left message to call me back on 21/03/2012	Needs to discuss with GUM
CSB	23/03/2012	09:01:00	Example Micro	01234 5678910	Microbiologist	Have received form and have no problems	Form fine
CSB	03/04/2012	16:01:00	Example Micro	01234 5678910	Microbiologist	Think GU have no problems	To confirm this
CSB	03/04/2012	16:05:00	Example GUM	01234 5678910	GUM	Left message to call me back	
CSB	03/04/2012	16:35:00	Example GUM	01234 5678910	GUM	All okay - will need to contact two patients	Await contact
CSB	23/04/2012	E-mail	Example GUM	01234 5678910	GUM	Couldn't leave message - have emailed to ask for outcomes	
CSB	01/05/2012	16:52:00	Example GUM	01234 5678910	GUM	Have left message to call me back	
CSB	11/05/2012	16:47:00	Example GUM	01234 5678910	GUM	Couldn't leave message - have emailed to ask for outcomes	
CSB	11/05/2012	Email	Example GUM	01234 5678910	GUM	Asked about last patient	Needs to look into it with Health Advisor
CSB	21/05/2012	14:49:00	Example GUM	01234 5678910	GUM	Left message with secretary	
CSB	28/05/2012	Email	Example GUM	01234 5678910	GUM	Asked about last patient	To check again
CSB	19/06/2012	16:38:00	Example GUM	01234 5678910	GUM	Asked about last patient	Will look into it
CSB	11/07/2012	14:34:00	Example GUM	01234 5678910	GUM	Not around today: back tomorrow	
CSB	11/07/2012	13:38:00	Example GUM	01234 5678910	GUM	No response from the two patients that they have tried to contact	
CSB	16/07/2012	16:38:00	Example GUM	01234 5678910	GUM	Left message for her to call back	Try again in two weeks
CSB	16/07/2012	09:38:00	Example GUM	01234 5678910	GUM	To speak to someone about last result	Will chase in one week
CSB	31/07/2012	12:38:00	Example GUM	01234 5678910	GUM	All finalised - last patient contacted	Finished!

B) Checklist for hospital microbiologist and clinician

Communication log for X Hospital				
Name of microbiologist	Example Micro			
Phone number	01234 5678910			
Email address	example@xhospital.nhs.uk			
Checklist for microbiologist				
Have they received the results	Y			
Do they any queries about them	N			
Are there any results which are not clear/any support needed for interpretation from Cathy Ison	N			
Clarify which patients they believe fit into each criteria (misdiagnosis, undertreatment, insufficient sample)	Y			
Ask them if they will contact the clinician and go through the results (when will this be)	Y			
Clarify the name of the clinician	Example GUM			
Clinician contact details				
	pt1	pt2	pt3	
Pt ID	ABCD1234	BCDE2345	CDEF3456	
Clinician name	Example GUM	Example GUM	Example GUM	
Clinician phone number	01234 5678910	01234 5678910	01234 5678910	
Clinician email address				
Checklist for clinician				
Checklist for clinician	y/n			
Ask them if they have received the materials	Y			
Ask them if they are clear on the criteria	Y			
Check that they have linked in with GUM and microbiologist	Y			
Ask them if they are clear which patients need contacting and for what reason e.g. misdiagnosis/undertreatment/insufficient samples	Y			
Ask them if they are clear how to communicate with the patient i.e. by phone first, and letter only if they can't get hold of the patient.	Y			
Check they have the right letter	Y			
If non-GUM ask them if they have linked in with GUM if the patient needs to be seen	Y			
Highlight that communication needs to be confidential and sensitive and NOT using communication methods that patients have requested not to use.	Y			

C) Hospital tracker to follow progress by region

SHA	Hospital	No. of samples testing positive with the affected batches	Further identified samples (Sept 2011)	Status of hospital investigation	No. of patients requiring retesting	No of pts mis-dx	No of pts mis rx	No of pts re rx	Pts affected	Samples not Ix or unclear	Patients	HPU
London	Hospital 1	48	3	Given near complete data	0	1	2	y	14	9		NECLHPU
	Hospital 2	92	8	Given near complete data	1	0	0	y	15	13		NECLHPU
	Hospital 3	16	0	Given near complete data	0	0	0	n	0			NWLHPU
	Hospital 4	61	0	Investigation completed	0	0	0	n	2	1		NWLHPU
	Hospital 5	155	10	Given near complete data	1	1	0	y	21	16		NECLHPU
	Hospital 6	146	5	Investigation completed	1	0	0	y	1	1		NECLHPU
	Hospital 7	43	2	Investigation completed	0	0	0	n	0			SELHPU
	Hospital 8	20	1	Investigation completed	2	2	1	y	0			SWLHPU
	Hospital 9	41	2	Given near complete data	0	1	1	y	2	2		SELHPU
	Hospital 10	5	1	Given near complete data	1	1	0	y	0			NECLHPU
	Hospital 11	82	3	Given near complete data	1	6	2	y	36	32		NECLHPU
	Hospital 12	132	5	Given near complete data	1	0	4	y	0			NWLHPU
	Hospital 13	13	0	Investigation completed	0	0	0	n	0			SELHPU
	Hospital 14	10	0	Investigation completed	0	0	0	n	0			NECLHPU
	Hospital 15	21	1	Investigation completed	0	0	0	n	0			NECLHPU
	Hospital 16	58	4	Given near complete data	0	0	0	n	4	3		SWLHPU
	Hospital 17	14	0	Investigation completed	0	2	0	y	0			SWLHPU
	Hospital 18	69	0	Investigation completed	0	0	0	n	0			SELHPU
	Hospital 19	1	0	Investigation completed	0	0	0	n	0			NECLHPU
	Hospital 20	64	2	Given near complete data	1	0	0	y	0			NECLHPU
	Hospital 21	8	0	Given near complete data	0	0	0	n	0			NECLHPU
South	Hospital 22	128	7	Given near complete data	1	2	0	y	29	17		KentHPU
	Hospital 23	65	8	Given near complete data	0	0	2	y	7	6		SurreySussexHPU
	Hospital 24	31	3	Given near complete data	0	0	0	n	6	4		SurreySussexHPU
	Hospital 25	43	1	Given near complete data	1	2	0	y	0		Confirm	KentHPU
	Hospital 26	70	6	Given near complete data	0	8	2	y	9	8		HampshireIOW
	Hospital 27	70	0	Investigation completed	0	0	0	n	0			ThamesValley
	Hospital 28	3	0	Investigation completed	0	0	0	n	0			HampshireIOW
	Hospital 29	77	3	Investigation completed	0	0	2	y	0			Thamesvalley
	Hospital 30	17	0	Investigation completed	0	0	0	n	0			SurreySussexHPU
Midlands and East of England	Hospital 31	33	3	Investigation completed	0	1	0	y	0			EssexHPU
	Hospital 32	41	0	Investigation completed	1	0	0	y	0			BedsHerts
	Hospital 33	6	0	Investigation completed	0	0	0	n	2	2		WestMidlandsNorth
	Hospital 34	31	1	Given near complete data	0	0	0	n	0			EssexHPU
	Hospital 35	72	0	Investigation completed	0	0	0	n	0			WestMidlandsEast
	Hospital 36	9	0	Investigation completed	0	0	0	n	0			WestMidlandsWest
	Hospital 37	351	0	Given near complete data	0	2	1	y	2	2		WestMidlandsEast
	Hospital 38	44	0	Given near complete data	1	0	0	y	1	1		EastMidlandsSouth
	Hospital 39	2	0	Investigation completed	0	0	0	n	0			EastMidlandsSouth
	Hospital 40	37	3	Investigation completed	0	0	0	n	0			BedsHerts
	Hospital 41	1	0	Investigation completed	0	0	0	n	0			BedsHerts
	Hospital 42	1	0	Investigation completed	0	0	0	n	0			WestMidlandsNorth
	Hospital 43	16	0	Investigation completed	2	0	0	y	0			WestMidlandsNorth
	Hospital 44	30	1	Given near complete data	0	0	0	n	0			NorfolkSuffolkCambridge
	Hospital 45	56	0	Investigation completed	1	0	0	y	0			WestMidlandsNorth
	Hospital 46	162	0	Investigation completed	0	0	0	n	0			WestMidlandsEast
	Hospital 47	6	0	Investigation completed	0	0	0	n	0			NorfolkSuffolkCambridge
	Hospital 48	104	0	Investigation completed	0	0	0	n	0			WestMidlandsWest
	Hospital 49	43	0	Investigation completed	2	0	1	y	0			BedsHerts
	Hospital 50	7	0	Investigation completed	0	0	0	n	0			NorfolkSuffolkCambridge
	Hospital 51	12	0	Investigation completed	0	0	0	n	0			WestMidlandsWest
Other	Hospital 52	2	0	Investigation completed	0	0	0	n	0			
	Hospital 53	8		Investigation completed	0	0	0	n	0			

Appendix 11: STBRL laboratory review report

As part of the ongoing investigation and management of the Level 3 HPA incident on false treponemal IgM results using certain batches of the Mercia Syphilis IgM kit the Incident Team agreed that a review of laboratory practices at HPA Birmingham should be undertaken by a laboratory group made up of two virologists from HPA Manchester, and Central Manchester Foundation Trust and a senior scientist and the Head of Quality from HPA Colindale,
Three members visited STBRL on 6 January 2012. One member was unable to attend on that day.

A member conducted a vertical audit of a reactive treponemal IgM assay (Mercia IgM) in the laboratory at Colindale with the help of two laboratory staff members.

Laboratory documentation was reviewed by three assessors, who then had a discussion with senior laboratory staff including the STBRL director about practices in the laboratory, including the quality system, and the false positive IgM incident itself.

Quality system
There is a very well developed mature quality system in place for the Colindale site overall. The documentation is of a high standard, with document control maintained through Q-Pulse. There is evidence of satisfactory document control within STBRL, with the ability to amend documents restricted to the STBRL Quality Manager (QM). An assessor had a separate discussion on the quality systems at Colindale with the Head of Quality for HPA Colindale, and with the STBRL QM.

The STBRL User Manual is comprehensive and of high quality. It details the tests available, the sample requirements including volumes, and the turnaround times.

The laboratory was fully CPA accredited at the time of the incident.

Testing protocols
At the time of the incident the laboratory was using the CE-marked Mercia Syphilis IgM EIA kit for treponemal IgM testing. The test protocol was documented in SOP No. G-6746/03-08 Enzyme immunoassay (EIA) for the detection of IgM antibody to *Treponema pallidum*. This had had a limited validation in accordance with SOP G-67009/02-08 Validation; validation was limited by lack of sera confirmed as having come from early syphilis cases.

The syphilis testing SOPs had been noted to be out of date in late 2011 (documented in the minutes of STBRL All Staff Meeting 17 November 2011).

STBRL used as the basis for its local testing algorithm the National Standard Method ‘Serological Diagnosis of Syphilis’ VSOP44 v1 issued on 9 November 2007 (Annex 1). This suggested testing with a treponemal IgM assay where samples were reactive in two treponemal tests (EIA and TPPA/TPHA).

Treponemal IgM testing became part of the routine testing protocol for evidence of syphilis infection on serum samples referred to STBRL. As STBRL receives virtually no samples for primary treponemal testing, it can be assumed that most samples coming to STBRL have been referred there because of initial reactivity in a treponemal test elsewhere, together with a small number of samples screening for evidence of congenital infection and for possible early infections wanting IgM testing. As a significant amount of time may have elapsed since the sample referred for testing was taken from the patient (because most samples tested by STBRL have already been tested at the referring laboratory and have then required transportation to STBRL) the local STBRL protocol became one of testing all four tests described in VSOP44 more or less simultaneously, with the aim of reducing turnaround times to a minimum at STBRL given the elapsed time before receipt of the sample at STBRL. The NSM algorithms allow for this type of flexibility.

In fact treponemal IgM became the first test done at STBRL testing because of the volume of serum required, followed soon after by EIA total antibody, TPPA, and RPR. This raised IgM status to a higher level than in the majority of laboratories. Nevertheless the caveats on IgM testing incorporated into V44 (formerly VSOP 44) - that IgM results must be interpreted with care because IgM may be long lived in syphilis, and that it may be nonspecific - were noted. The interpretative comments issued on STBRL reports were satisfactory in reflecting this and in requesting a sample in cases of IgM reactivity.

However there was a departure from the recommended comment in V44 at STBRL. The V44 comment ‘Consistent with recent or active treponemal infection’ had been altered by STBRL to read ‘Consistent with recent or acute treponemal infection’. The STBRL comment perhaps gives more weight to an infection being ‘acute’, thereby suggesting more recent and current infection than the suggested V44 comment which implies that active infection regardless of duration may produce positive RPR/VDRL and/or IgM.

Vertical audit

A vertical audit was conducted taking a sample reactive for treponemal IgM during the incident period. The preanalytical, analytical and postanalytical processes were examined. All documentation reviewed showed evidence of document control.

CPA E standards were met in having a satisfactory user manual widely available electronically, including advice on specimen collection, a satisfactory request form, and accurate transcription of information into the laboratory computer system. Standard E5.1c was not met in there being limited audit data in determining time from sample receipt to testing in the absence of a process of time and date stamping on receipt. The sample had been appropriately labelled and had been retained in a temperature-monitored freezer; it was readily available (standard A10.2). The sample reception area was satisfactorily laid out and procedures for specimen receipt and rejection, and referral were available (E5, E6). Reagent labelling and storage was appropriate and stock control maintained the materials in date. Biomedical scientists performing the testing were appropriately trained, with documented records of training, signed off, and evidence of maintenance of CPD.

The examination, treponemal IgM testing, had been validated before use in accordance with SOP on validation. Validation has been limited by the lack of access to sera from proven cases of early syphilis. The test in use at the time was documented under SOP No. G-6746/03-08, (effective date 07.01.08, review date 07.01.2011) which was not available in the laboratory at the time of the visit as it had been withdrawn from use (archived on Q-Pulse after its withdrawal

on 04.01.12). Its replacement G-6746/04-12 was available both electronically and in hard copy (review date 04.01.2015).

Result reporting is through the MOLIS system, and the process was well documented and robust. A copy of the test report could be generated and there was a full audit trail. Interpretative comments are included and reporting follows both technical and consultant validation. Report validation at technical and medical authorisation levels is covered in the SOPs.

The three day turnaround time stated in the User Guide for testing was met. The User Guide is available online at http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317133788262

Quality Control
Quality control parameters appeared satisfactory and were written into the SOP. The quality system is managed centrally from Prof Sharp's office.
IQC

IQC results are well recorded. IQC failures are reported as nonconformances (F3.2) and reviewed at monthly staff meetings.

Levey-Jennings plots were available for the assays covering the period before, during and after the incident and showed nothing out of the ordinary, with no evidence of systemic failure.
The laboratory participated in the NEQAS scheme for treponemal serology, with satisfactory performance. The NEQAS scheme does not however test treponemal IgM performance. There was no evidence of the laboratory participating in an exchange of IgM reactive/nonreactive samples to deliver an ad hoc EQA scheme although there was evidence that this was being actively considered.

Routine maintenance of equipment was satisfactory but the automated DS2 analyser on which the treponemal IgM should have been run had had regular failures; this had led to delays in testing and the necessity to move to potentially less reproducible manual testing. This was felt to contribute to the delay in recognising the problem.

EQA
The laboratory participates in the EQA scheme for treponemal serology run by UK NEQAS. The scheme does not include a specific treponemal IgM serology component, although IgM reactive samples may be included. STBRL had recognised this as a concern and had tried to organise an exchange of sera with a South African laboratory (STBRL All Staff Meeting 29th September 2011 minutes).

IQA
The laboratory had a robust scheme for carrying out IQA by retesting samples, selecting ten per month. This had generally run well and had showed no significant errors on review; testing had only lapsed in September 2011 due to staff absences and the pressures of the treponemal IgM incident.

Appendix 12: Incident debrief

Methods
Feedback regarding the incident was received through three sources:

- An incident team structured debrief teleconference 14 June 2012, coordinated by a London REU public health trainee
- Incident team members who were unable to attend the debrief teleconference and senior HPA colleagues were asked to feedback separately by email or use of a select survey tool.
- All the acute Trusts who were involved in the investigation were asked to feed back using a select survey tool.

Incident team debrief

Roles
Although there was fluidity in roles over the course of the investigation there was no role confusion. It was felt that everyone understood their roles and was aware of and understood others roles too.

Team working and engagement
The group were unanimous in their praise for the dedication and hard work of the core incident team. The significant work carried out by Microbiological Services (MS) staff, in particular the Sexually Transmitted Bacteria Reference Laboratory (STBRL) staff was also acknowledged.

The staff involved have gone well above and beyond regular working patterns with many additional unpaid hours to ensure support for the incident.

There was good team working across the various sections of the HPA involved in response to the outbreak. Cross-border working was also good with strong relationships with colleagues in Devolved Administrations. Both HPS and MS supported the whole investigation and remained engaged with the process throughout.

It was felt that although they had raised the alarm over the kits initially STBRL had received an unnecessary and unwarranted amount of criticism over what some perceived as delays in responding to the problem. This had produced a negative atmosphere and some disruption in STBRL, as staff felt that the quality of their work was being called into question.

Timeframes/expectations
There was a high level of support and interest in the incident by senior management/executive group members. However it was also felt that the complexity of the incident was not initially appreciated and that there was perceived pressure from senior management to complete the investigation quickly.

Reporting back to multiple senior groups in different formats was seen as a distraction at times. Early reporting expectations were not met due to a lack of clarity of requirements.

Complexity
As mentioned above, this incident and the required response were very complex. The complexity of the incident meant that some decisions on the protocol for the investigation were very difficult to make. This did result in some decisions being altered or apparently reversed after they had been communicated initially.

Some of the feedback received prior to the meeting suggested that some of the complexity was introduced by the attempt for completeness in the review of cases, which was in turn perceived to be driven by a desire to avoid missing any patient, and the potential for adverse media reaction.

It has been suggested that a more “common sense” approach should have been taken, for example by retesting everyone rather than trying to risk assess and retest on an individual basis. However those members of the incident team present for the verbal debrief felt that the protocol followed in the end was the appropriate balance given the risk assessment.

Communications
Overall the communications aspects of the incident response were rated highly, with the incident team and wider stakeholders indicating their confidence in the HPA communications team.

The decision on media strategy – to be reactive or proactive – was given careful consideration. The decision to have a proactive media strategy was however felt to be the correct one as it allowed the key messages to be delivered clearly and meant the information was well-managed.

It was reported that there was more media interest in Scotland than elsewhere. It was raised that initially some of the initial communications were not circulated to the devolved administrations. This emphasised the importance of having the right people around the table including the national leads and representatives of the devolved administrations.

It was felt that the target of communications could be refined. Most of the communication with professionals was channelled through local microbiologists. It was felt that direct communication with responsible senior management, such as medical directors, would have provided better levers for completion of the look back exercise. It was also fed back that the frontline clinicians involved would have liked direct briefing alongside, rather than through, their microbiology colleagues.

Resourcing
The use of shared IT facilities (shared drive, common email inbox) was a benefit to the efficiency of the incident response.

Participants believe that there is further work to be done around capacity building and resilience for future incidents of this type. It was felt that it would have been simpler to pull in additional trained staff in an outbreak situation rather than a look back or other incident.

Key to this is identifying availability and skills sets of staff and building up expertise. In particular the issue was raised that any additional staff drafted in to help with re-testing would have to already be specialist in this area, or would only slow down the investigation process. It

was suggested that spare capacity at other national/regional laboratories could be used in these circumstances.

It was also recognised that there was a need to balance the need for internal capacity and the availability of training opportunities for registrars and other rotational staff.

Areas where consideration should be given to staff resource:
- Sitrep and other report production is a whole role in itself
- need for a dedicated information officer to manage complex data
- more administrative support would have been welcomed

Other comments
The following comments were also made related to other aspects of the incident response:
- lack of authority/powers of MHRA in relation to enforcement of quality standards a concern
- importance of ensuring legal protection for incident response by early involvement of legal team
- laboratory codes raised some issues; single trusts had multiple codes and the names were not always up to date
- duty to act in a way compatible with responsible stewardship of public funds
- process of protocol production takes time – flowchart and ‘road testing’ very helpful
- lack of resilience in DGH microbiology – incident response passed to junior staff in some instances
- limited patient feedback but reaction generally positive
- balancing priorities with other time sensitive duties by some ICT members, particularly Olympics planning
- national serum bank would help validation and control of tests

Feedback from microbiologists and clinicians
Responses to an online survey were received from 15 GUM clinicians or microbiologists. Individual comments can be found in Addendum 1:

Recommendations
- when needing a significant response from acute trusts then communicate directly with the medical director
- for complex incidents requiring a non-acute/critical response from many external agencies expect many delays and build these into realistic timeframes for milestones
- involve the legal department at an early stage
- important to have the right people in the incident group and more than one person fulfilling each role where possible for long incidents where they not be available for every ICT eg two GUM clinicians
- clear lines of accountability should be ascertained at the beginning
- clarify early on with senior teams such as the Executive Group, Senior Management Teams what their expectations were for situation reports and briefings, including agreed timing, content and format
- if time allows, a period of reflection on significant decisions may be beneficial
- prospectively record the additional work taken on e.g. count hours, to identify opportunity costs of the incident management
- shared IT facilities (email, shared storage spaces) are essential

- identify sufficient information officer resource when large and/or complex data handling is involved
- involve permanent members of staff where possible for additional experience and exposure in complex incidents
- pilot protocols with clinicians/staff not intimately involved in the incident
- early involvement of local HPU support for national incidents where a prompt local response is needed

Addendum 1

What went well
Good co-ordination
Good communication after notification
Personal telephone communication with coordinators
HPA easily contactable and helpful throughout
Kept up to date of progress
Regular communication via e-mail
Template letters sent
Secure access to patient information
Need to check spelling of names of people being contacted to minimise errors
Help from HPA
Helped to make sense of previous odd results
Thorough
Persistent
Well organised
Good communication
Clear direction
Written documentation forwarded to us (hard copy)
Email support
Telephone support
Email communication
Secure transfer of data through "encrypt" emails on hpa.org.uk
Incident team took a lot of the phoning and chasing of responses upon themselves
Safeguarded patients who were involved
Investigations and findings prevent future incidents such as this
This educated us how we should investigate
Data collection and presentation
Working with HPA staff
Prepared documents
You have retested samples with only IgM positive result or 2/4 tests positive
Communication
Our GUM specialists have done right assessment based on clinical findings and laboratory results
Good dissemination of information
Identification of all patients tested who required further investigation
What could have done better
Very slow to notice a problem with kit
Earlier notification
Faster re testing
E-mail communication of what to do with the cases identified needing contacting
Scheduling/timeframes for meetings were tight at a time of public holidays/Christmas

Slight assumption that HPA was only lab involved, eg pressure from HPA press office to change our press statement to fit with HPA one
Had to re-send data due to error on initial datasheet sent by HPA
Incorrect spelling of lead clinician
Forms very confusing - could be simpler
Direct contact with clinicians - I received all my initial info via microbiologist
Focus on those patients that may need additional treatment - not initially clear
More flexibility for getting feed-back from our users
Not involving senior trust management to pressurise lab staff
IT filling in the results section was problematic
A lot of repetition of information
Short time line initially.
Identifying and clarifying the role of all those involved in the initial stage
Electronic version of patients' results to be rechecked not easily accessible
Guidance on how to proceed initially when problem was identified
Not so many changes in decisions
Keep it more simple
Being less strict about a specific date when everybody needs to be informed at the same time
HPA didn't know who to pass on the information in the laboratory
Various persons alls chasing the same things
Direct communication with GUM clinicians
Strategic approach - would it not have been easier to simply retest all at outset
Prepared documents came out late in the process
Not to send everything just before Christmas. Most of the doctors were not available to contact
To retest ALL samples if enough material before sending reports to us
It took a long time from the first information re problem with IgM test until final letter came out
A bit more information about the delays and when to instigate recall etc.
What would you recommend to improve response in the future
Faster notification
Faster re testing
Have a named person for each geographical area and conduct exercise by personal telephone communication aided by e-mail if necessary
Suggest check datasheet meticulously prior to sending out
Need to check spelling of names of people being contacted to minimise errors
A clinician meeting to focus on what we are trying to achieve
Pilot forms with real clinicians
Continue close contact with HPA
Clear line of communication
Electronic version of results to be more accessible
Prompt availability of guidance
More common sense and less worry about possible media criticism if one case is missed
Shorter telephone conferences
Send out short summaries - there were too many documents which made things confusing
Establish clear communication links
Most of the information required was from Gum clinicians
Gum clinicians weren't notified directly.
Asking for treatment information meant that there were many questions from the clinicians that could not be answered at that time

Appendix 13: MHRA Medical Device Alert

Laboratory based syphilis test: Mercia Syphilis M kit manufactured by Microgen Bioproducts Limited (MDA/2011/104):
www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON134779

MHRA

Medical Device Alert

Ref: MDA/2011/104 Issued: 03 November 2011 at 14:30

Device

Laboratory based syphilis test.

Mercia Syphilis M kit manufactured by Microgen Bioproducts Limited.

Lots 052X1, 053X1 and 05411A.
Product code: M404.

Problem

Higher level of non-specific cross-reactivity leading to false positive syphilis IgM results observed with lot numbers 052X1, 053X1 and 05411A.

This may lead to misdiagnosis of early acute infection.

Action by

Reference laboratories.
Directors of pathology.
Biomedical scientists (microbiologists).

Action

- Do not use affected lots.
- Routine diagnostic microbiology laboratories and confirmatory laboratories that have used the affected lots should consider the need to review previous positive results.
- Laboratories undertaking confirmatory testing should consider informing referring laboratories of your review where relevant.
- Laboratories that have received results from confirmatory laboratories should examine the reporting comments. If there are any positive IgM-only results, repeat samples must be requested for these.
- Contact your confirmatory laboratory or the HPA Sexually Transmitted Bacteria Reference Laboratory (STBRL) for advice on a suitable approach to risk assessment.

CAS deadlines

Action underway: 10 November 2011

Action complete: 05 December 2011

Contact

Manufacturer
Christopher Rackham
Microgen Bioproducts Ltd
Tel: 01276 600 081
Fax: 01276 600 151
Email: crackham@microgenbioproducts.com

Medicines and Healthcare products Regulatory Agency Page 1 of 9

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Device

Mercia Syphilis M is an IgM antibody class capture immunosorbent assay for the detection of Treponema pallidum-specific IgM in human serum, which in combination with T pallidum IgG assays can be used in differential diagnosis between past and active syphilis infection. This notice does not apply to the Mikrogen recomWell IgM assay.

Action

Additionally, the Health Protection Agency (HPA) incident response group advises that:

- syphilis IgM positive results should be tested by at least one additional treponemal test (EIA/TPPA) and a non-treponemal test (RPR/VDRL)
- results of syphilis IgM tests used in isolation should be interpreted with caution and correlated with other test parameters and the likelihood of infection.

Problem

Microgen Bioproducts issued two Field Safety Notices (see appendix) warning that product performance studies with a primary reference panel of sera indicated that the three lots of Mercia Syphilis M kits (lots 052X1, 053X1 and 05411A) exhibit a higher than expected level of false positive results.

These three lots were on sale from 19 October 2010 to 3 October 2011 inclusive.

The investigation into the root cause of this issue is ongoing.

Distribution

This MDA has been sent to:

- NHS trusts in England (Chief Executives)
- Health Protection Agency (HPA) (Directors)
- HSC trusts in Northern Ireland (Chief Executives)
- NHS boards in Scotland (Equipment Co-ordinators)
- Local authorities in Scotland (Equipment Co-ordinators)
- NHS boards and trusts in Wales (Chief Executives)
- Primary care trusts in England (Chief Executives)

Onward distribution

Please bring this notice to the attention of relevant employees in your establishment. Below is a suggested list of recipients.

Trusts

CAS and SABS (NI) liaison officers for onward distribution to all relevant staff including:

- Antenatal screening coordinators
- Biomedical science departments
- Clinical pathologists
- Clinical pathology directors
- Directors of genitourinary medicine clinics
- Genitourinary outpatient clinics
- GUM physicians
- Infectious disease wards
- Medical directors
- Microbiologists
- Purchasing managers
- Risk managers
- Special care baby units
- Supplies managers

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Health Protection Agency
Directors for onward distribution to:
- Collaborating centres
- Consultants in communicable disease control
- Divisional directors
- Heads of health, safety and quality
- Health protection nurses
- HPA laboratories
- Laboratory managers
- Regional directors
- Regional microbiologists
- Risk manager
- Safety officers

Primary care trusts
CAS liaison officers for onward distribution to all relevant staff including:
- Directors of public health
- General practitioners
- Health visitors
- Immunisation co-ordinators
- Infection control nurses
- Practice managers

Independent distribution

Establishments registered with the Care Quality Commission (CQC) (England only)
This alert should be read by:
- Clinics
- Hospitals in the independent sector
- Independent treatment centres
- Private medical practitioners

Please note: CQC and OFSTED do not distribute these alerts. Independent healthcare providers and social care providers can sign up to receive MDAs directly from the Department of Health's Central Alerting System (CAS) by sending an email to: safetyalerts@dh.gsi.gov.uk and requesting this facility.

Contacts

Manufacturer
Christopher R Rackham
Operations Director
Microgen Bioproducts Ltd
1 Admiralty Way
Camberley GU15 3DT
Tel: 01276 600 081
Fax: 01276 600 151
Email: crackham@microgenbioproducts.com

England

If you are in England, please send enquiries about this notice to the MHRA, quoting reference number **MDA/2011/104** or **2011/009/001/081/006**

Technical aspects
Mojisola Ajeneye or Rosalind Polley
Medicines & Healthcare products Regulatory Agency
Floor 4
151 Buckingham Palace Road
London SW1W 9SZ
Tel: 020 3080 7271 / 7119
Fax: 020 8754 3965
Email: mojisola.ajeneye@mhra.gsi.gov.uk
rosalind.polley@mhra.gsi.gov.uk

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Clinical aspects
Dr Nicola Lennard
Medicines & Healthcare products Regulatory Agency
Floor 4
151 Buckingham Palace Road
London SW1W 9SZ

Tel: 020 3080 7126
Fax: 020 8754 3965

Email: nicola.lennard@mhra.gsi.gov.uk

Health Protection Agency Contact
Dr Colin Brown
HPA Centre for Infections
The Sexually Transmitted Bacteria Reference Laboratory (STBRL)
61 Colindale Avenue
London NW9 5HT

Tel: 020 8327 7563

Email: colin.brown@hpa.org.uk

How to report adverse incidents

Please report via our website http://www.mhra.gov.uk
Further information about **CAS** can be found at https://www.cas.dh.gov.uk/Home.aspx

Northern Ireland

Alerts in Northern Ireland will continue to be distributed via the NI SABS system.

Enquiries and adverse incident reports in Northern Ireland should be addressed to:

Northern Ireland Adverse Incident Centre
Health Estates Investment Group
Room 17
Annex 6
Castle Buildings
Stormont Estate
Dundonald BT4 3SQ

Tel: 02890 523 704
Fax: 02890 523 900

Email: NIAIC@dhsspsni.gov.uk

http://www.dhsspsni.gov.uk/index/hea/niaic.htm

How to report adverse incidents in Northern Ireland

Please report directly to NIAIC, further information can be found on our website http://www.dhsspsni.gov.uk/niaic
Further information about **SABS** can be found at http://sabs.dhsspsni.gov.uk/

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Scotland

Enquiries and adverse incident reports in Scotland should be addressed to:

Incident Reporting and Investigation Centre
Health Facilities Scotland
NHS National Services Scotland
Gyle Square
1 South Gyle Crescent
Edinburgh EH12 9EB

Tel: 0131 275 7575
Fax: 0131 314 0722

Email: nss.iric@nhs.net

http://www.hfs.scot.nhs.uk/online-services/incident-reporting-and-investigation-centre-iric/

Wales

Enquiries in Wales should be addressed to:

Dr Sara Hayes
Senior Medical Officer
Medical Device Alerts
Welsh Assembly Government
Cathays Park
Cardiff CF10 3NQ

Tel: 029 2082 3922

Email: Haz-Aic@wales.gsi.gov.uk

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Appendix

MICROGEN BIOPRODUCTS LIMITED

1 Admiralty Way

Camberley

Surrey GU15 3DT

United Kingdom

Telephone: +44 (0)1276 600 081
Fax: +44 (0)1276 600 151

Name and Address

28 October 2011

Urgent – Field Safety Notice:

Subject: Mercia Syphilis M; Product Code M404CE Lot 05411A

Dear

We have identified a problem with Syphilis M kit Lot 05411A which exhibits a lower specificity than normal, meaning there is an increased risk of false positive Syphilis IgM results.

This Safety Notice supplements the one sent on 24th August 2011 but relates to a lot number that we had previously excluded from that notice.

Our advice is that:

1) Lot 05411A should not be used.
2) Positive results obtained with this lot should be confirmed by an alternative method if possible.
3) Laboratories should consider the need to review IgM positive only results obtained with this lot

Please confirm receipt of this communication and indicate the number of kits remaining in your inventory by faxing back or e mailing page 2 of this communication. We will provide credit or replacement product for these.

Microgen (or where appropriate your Microgen distributor) will be contacting you shortly to discuss the future supply of Syphilis M kits. We have an alternative Syphilis IgM Capture kit available, which has been independently developed and is manufactured by our parent company Lab 21.

Please accept our apologies again for this situation which we are working hard to resolve.

Yours sincerely

Christopher R Rackham

Website: www.microgenbioproducts.com Registered in England number 2832020

αβχδεφ

Issued: 03 November 2011 at 14:30 Ref: **MDA/2011/104**

Operations Director

Customer Name
Address

To: **C Rackham, Microgen Bioproducts**

FAX: **01276 600151**
E mail: **crackham@microgenbioproducts.com**

I confirm receipt of Microgen Product Safety Notice dated 28 October 2011.

The number of Mercia Syphilis M kits we have remaining in inventory are:

Lot 05441A .....

Signed ..... Date .....

Website: www.microgenbioproducts.com Registered in England number 2832020

αβχδεφ

Issued: 03 November 2011 at 14:30 Ref: **MDA/2011/104**

MICROGEN BIOPRODUCTS LIMITED

1 Admiralty Way

Camberley

Surrey GU15 3DT

United Kingdom

Telephone: +44 (0)1276 600 081
Fax: +44 (0)1276 600 151

Customer Name
Address

24 August 2011

Dear

Urgent - Product Safety Notice:
Product Code M404 Mercia Syphilis M kit lots 052X1 and 053X1

We have received one report from a user of lot 053X1 Mercia Syphilis M (Product code M404) of false positive Syphilis IgM results.

Further product performance studies with a primary reference panel of sera indicates that the two lots of Mercia Syphilis M kits (Lots 052X1, and 053X1) exhibit a higher level of false positive results than normal.
These two lots have been on sale from 19 October 2010 to 25 May 2011 but the report of false positive reactions has only recently been received and investigated. A later lot (05411A) does not exhibit this problem.

Given this situation we would specifically draw your attention to the precautionary statements in section 11 of the Instructions For Use as follows:

- Diagnosis of an infectious disease should not be established on the basis of a single test result. A precise diagnosis, in fact, should take into consideration clinical history, symptomatology, as well as serological data. Serological data, however, have restricted value in immunosuppressed patients.
- To estimate (primary or recurrent) *T.pallidum* infections by serology it is advised to test serum pairs. The second serum of a pair can be drawn 14-21 days after the first serum is obtained. Each serum pair should be tested on the same day and in the same test run to allow interpretation of significant antibody level differences. It is advised to perform a combination of IgM and IgG testing.
- In a clinical evaluation this *Treponema pallidum* IgM EIA showed reactivity with some of the following interfering sera: ANA-IgM, Epstein Barr Virus IgM, Borrelia IgM and Parvo-B19 IgM.

Our further advice is as follows:

1. Please confirm receipt of this communication and detail the number of kits remaining in your inventory of these two lots by faxing or e mailing back page 2 of this letter.
2. Do not use remaining kits from these lots in your inventory. Any positive results should be confirmed by an alternative method. Microgen will replace these kits free of charge as soon as we have manufactured a new lot (estimate 2- 3 weeks).

Website: www.microgenbioproducts.com Registered in England number 2832020

Issued: 03 November 2011 at 14:30 Ref: **MDA/2011/104**

Please accept our apologies for this situation. The quality of our products is of paramount importance to us and we are working hard to make sufficient replacement material available to you as soon as possible.

Yours sincerely

Christopher R Rackham
Operations Director

.....

Customer Name
Address

To: **Customer Services, Microgen Bioproducts**

FAX: **01276 600151**
E mail: customerservices@microgenbioproducts.com

I confirm receipt of Microgen Product Safety Notice dated 24 August 2011.

The number of Mercia Syphilis M kits we have remaining in inventory are:

Lot 052X1 .....

Lot 053X1 .....

Signed ..... **Date** .....

Website: www.microgenbioproducts.com Registered in England number 2832020