Warwick Medical School

Detection & Identification of Infectious Agents (DIIA)
Innovation Platform: Health Econometrics

ECONOMIC ANALYSIS REPORT

Point of Care Tests for Hospital-Acquired Infections (HAIs)

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Research Team:
Professor Ala Szczepura, Warwick Medical School
Dr Leeza Osipenko, Senior Scientific Adviser, Scientific Advice Team, NICE & Honorary Fellow Warwick Medical School

Contact:
Ala Szczepura, Professor of Health Services Research,
Warwick Medical School, University of Warwick, Coventry CV4 7AL
ala.szczepura@warwick.ac.uk

Detection & Identification of Infectious Agents (DIIA) Innovation Platform: Health Econometrics

Area: Hospital Acquired Infections (HAIs)

1. BACKGROUND

A number of clinical/disease areas have been prioritised by the Technology Strategy Board (TSB) and Department of Health (DH) for the DIIA Innovation Platform. To support commissioning of technology development for detection of hospital acquired infections (HAIs) in humans, a scoping review has been undertaken to help identify the specific requirements for new diagnostic test development and likely economic payback for point of care (POC) tests for HAIs in the UK.

This report presents economic analysis findings for the following HAIs:

- Methicillin-resistant Staphylococcus aureus (MRSA)
- Clostridium *difficile* (C. *difficile*)
- Extended-spectrum beta-lactamase (ESBL) infections.

2. FRAMEWORK

An evaluative framework was developed within which any new POC diagnostic technology could be considered. The final framework was agreed with the TSB and Department of Health. The study adopted a pre-defined methodology. The health economics team undertook literature reviews, evidence synthesis, and economic modelling/early-health technology assessment (HTA) of POC tests for each infection type. Independently, a scientific team examined the characteristics of existing laboratory tests for these infections and outlined the performance parameters required for an 'ideal' POC test. These ideal test parameters were then used in economic modelling, along with evidence from the literature review.

The health economic scoping study was based on two main elements: (i) **UK burden of illness:** estimation of national costs associated with each infection (including mortality, morbidity and treatment costs) and the cost of diagnosis and screening using current tests; (ii) **UK economic model:** POC testing scenarios were mapped against existing tests to estimate any clinical or cost consequences (on positives detected, false negatives/false positives reported, infections transmitted, and healthcare and mortality costs) and the likely impact of widespread POC test introduction was estimated. The main analysis focused on estimating incremental direct costs on moving from current tests to a new POC test. For different scenarios, the model estimated the total cost of resource use and the number of infections detected. Historical costs extracted from the literature were inflated to 2007/08 prices. A one-day workshop was held in which preliminary findings from the model were presented to national experts. The model was then further refined based on expert opinion and additional information provided by group members. The model excluded longer term impact on antibiotic resistance which is difficult to quantify robustly in monetary terms.

3. ECONOMICS

3.1 Hospital-acquired infections (HAIs)

There has been considerable growth in literature on the economics of various hospital-acquired infections (HAIs) in recent years. This is thought to be due both to a need to understand the financial implications of HAIs, and because of pressure to demonstrate the cost-effectiveness of infection control systems.[1] At the same time, it is acknowledged that there is a need to develop more sophisticated policy models for estimating the economic impact of HAIs and evaluating the cost-effectiveness of interventions designed to reduce these[2].

The present report focuses on infections acquired in hospitals. Assessment of the economics of infections acquired in other institutions such as care homes is outside the remit of the present report; this **represents an important gap** in any discussion of new point of care (POC) tests. The care home sector (residential and nursing homes) is an important provider of care for older people. There are currently 441,000 beds for adults in 19,000 care homes in England; this compares with 167,000 beds in the hospital sector.[3] Annual expenditure by local authorities on personal care services for care home residents is currently estimated at £4.8 billion (2004/5) with spend predicted to rise more rapidly than on home care.[4] The Department of Health is currently updating its guidance on infection control in care homes; a final version is not yet available.[1]

3.1.1 HAIs: Economic burden of disease

In the USA HAIs represent the fifth leading cause of deaths in hospital, and the financial burden is estimated at $6.5 billion ($7.08 billion, 2007 prices) per annum.[2] In the UK, HAIs have been reported to be a contributory factor in more than 5,000 deaths per year [5], with an estimated 300,000 cases in 2001.[6] An in-depth UK study identified a 13% death rate for inpatients with an HAI; compared to 2% for those without. Even after adjusting for patient demographics, clinical condition etc, individuals who acquired an infection were reported to be 7.1 times more likely to die.[7]

Nationally, it has been estimated that HAIs add £986.4 million (£1.3 billion, 2007 prices) to NHS costs.[7] The most recent NAO report similarly quotes an annual cost for all HAIs in excess of £1 billion [5]; this figure is not expected to change in the revised version[2] Post-discharge costs represent a small proportion of this total figure; downstream costs for outpatient visits total £26.8 million, GP follow up £8.4 million, and district nurse visits £20.5 million. The majority of the impact on hospital cost (£507.77 million, 55%) is associated with multiple infections. For single infections, UTIs represent the largest economic burden for the hospital system (£160 million in total, 2007 prices), the burden from surgical site infections (SSIs) is lower (£81million, 2007 prices), and blood stream infections on their own represent additional costs of £33 million (2007 prices).[7] These figures exclude compensation paid out by the NHS to victims of MRSA and *C. difficile*. This was reported to be almost £7.5 million in 2007/08, with a further £42 million NHS Litigation fund for cases still pending.

Because many of the costs quoted above are based on 1995 data, even after inflation to current prices they probably underestimate the current cost of HAIs following the rise in MRSA and *C. difficile* cases since 1995. A recent US analysis has identified overall annual direct hospital medical costs of between $28.4 and $45 billion per annum (2007 prices) for all HAIs. After adjusting for

[1] Personal communication, Dr C Bowman, Medical Director BUPA Care Homes.

[2] Personal communication, NAO.

the range of effectiveness of possible infection control interventions, the benefits of prevention are estimated to range from a low of $5.7 to $6.8 billion (20 percent of infections preventable) to a high of $25.0 to $31.5 billion (70 percent of infections preventable).[8]

3.1.2 HAIs: Cost of current treatment and control

Approximately one in ten of all patients in an NHS acute hospital will acquire an HAI.[9] Post discharge, it has been reported that a further 19% who were negative in hospital will report an infection.[7]

A recent review of economic analyses of general HAIs has identified that the quality of papers is generally poor.[2] Numerous studies indicate that HAIs are associated with increased length of hospital stay, and also worse outcomes for patients.[7, 10-15] In general, the highest incremental cost per patient is reported for bloodstream infections or bacteraemia.[10, 11] Standardising published results, a mean extra cost per patient of $36,441 (£19,199, 2007 prices) is estimated for blood stream infections.[2] Surgical site infections (mean $25,546; £13,459, 2007 prices) and ventilator assisted pneumonia (mean $9,969, £5,252 2007 prices) have the next highest incremental cost. A single UTI in general adds least to the cost of a hospital stay (mean $1,006; £530, 2007 prices).

In the UK, an average cost of £4,400 (2007 prices) per patient is reported for general HAIs; this figure includes staff, treatment and overhead costs.[7] Analysis by infection site indicates that general blood stream infections add the most at £7,600 per case; respiratory infections add £3,400; and surgical wound infections £2,300. Multiple site infections add the greatest cost to a hospital stay (£13,000, 2007 prices).

Only one UK study provides information on costs incurred after discharge.[6, 7] These are £58 per patient for infections diagnosed prior to discharge, and £23 for infections only reported post-discharge. Personal costs, time off work and informal carer costs add a further £832 for infections diagnosed before discharge, and £441 for those occurring post-discharge.

3.2 MRSA: Economic disease burden & testing and treatment costs

Summary figures for the calculations below are presented in **Table 2**.

3.2.1 MRSA: Economic burden of disease

In the UK, MRSA is among the HAIs of highest economic concern.[16] The proportion *S. aureus* isolates that are methicillin resistant is ≥ 25% [17]. In other countries, levels are lower (<3%) in Scandinavia, Switzerland and the Netherlands; similar (> 30%) in Spain, France, Italy and Portugal; and much higher in the USA (64%) and Japan (74%).[9]

The economic burden associated with MRSA is likely to decrease in the UK. Figures for bacteraemia (~25-30% overall mortality [18, 19]) have shown a significant fall from 6,383 cases in 2006/07 to 4,450 in 2007/08 following government initiatives.[20] With the introduction of MRSA screening for all hospital admissions by 2011, this trend is likely to continue. Therefore, although we present current data below, we suspect that figures may need to be adjusted down to accommodate declining rates of hospital acquired MRSA.

MRSA mortality:
The number of deaths mentioning MRSA in England and Wales increased from 51 to 1,652 between 1993 and 2006.[21] In 2007, 460 death certificates in England and Wales reported that MRSA was the underlying cause of death, and a further 1,133 mentioned it as a contributory cause.

However, a confidential report found considerable under-reporting of MRSA on death certificates (~35% reported).[22] This would indicate a 'true' figure of 1,314 deaths, rather than 460.

The age profile for MRSA deaths in 2007 shows 1,104 (69%) in the 85 and over age group, 429 (27%) in the 45-85 group, and 60 (4%) in the under 45 age group.[21] Applying this age profile, together with the average UK life expectancy of 79.4 years [23], to the 460 MRSA deaths in 2007 we estimate ~2,560 Life Years (LYs) lost. This equals a mortality cost of ~£69 million per annum in England and Wales (assuming health related quality of life (HRQoL) of 0.7; life year valued at £38.8k, discount rate not applied). For a 'true' figure of 1,314 deaths, the **mortality cost would rise to ~£198 million p.a.** as shown in **Table 2**.

MRSA morbidity:
It is not possible to estimate the UK morbidity burden associated with hospital acquired MRSA. The annual number of infections required to calculate this cannot be identified accurately. Only bacteraemia figures are routinely reported, but MRSA wound infections are known to be four times higher than bacteraemia [24], with MRSA now accounting for 24% of all surgical site infections.[25] Totalling wound infection and bacteraemia numbers indicates at least 22,250 MRSA infections in England in 2007/08; this excludes infections detected in other samples such as urines and catheters.

An alternative way of estimating an upper MRSA figure is to start with the 15.7 annual hospital admissions in England. Based on a reported 7% prevalence rate [9, 26-29], it can be estimated that ~1 million patients will enter hospital each year colonised with MRSA. Studies suggest that 20-60% of these admissions will go on to develop an MRSA infection.[30, 31] Taking the lower figure of 20% would suggest a total of ~200,000 MRSA hospital infections annually in England if these patients are not decolonised.

Even if this figure could be estimated accurately, it is not possible to estimate the number of QALYs lost and therefore a morbidity cost since the impact on HRQoL for individuals following an MRSA infection has not been reported in any studies.

MRSA costs to society:
In the UK, a loss of between **£3 billion and £11 billion annually** to the economy has been reported due to MRSA, to include a real fall in gross domestic product through lost work/output.[32] Another study estimates that between £300 million and £1,750 million worth of UK healthcare and social services are lost each year due to MRSA.[33] In the USA, the cost has been estimated at between $US17 billion and $US30 billion, discounting the costs of litigation.[34]

3.2.2 MRSA: Cost of current treatment and control

For the calculations below, **Annex 1a** provides an overview of input parameters and assumptions used to estimate costs.

MRSA inpatient care:
Estimating the extra cost associated with hospital acquired MRSA is difficult because attributing an incremental cost to these HAIs will be confounded by case-mix and severity of the patient's underlying condition.[34, 35] Not all published studies control for these factors. The global cost to the NHS due to MRSA infections has been reported as more than £45 million per annum.[36] There is agreement that the main cost driver is the impact on hospital length of stay.[37, 38] Isolation policies can also increase costs significantly with an isolation cost (over and above standard bed day costs) of about £50 per patient/day.[15, 39, 40] Contact precautions (antiseptic hand washing, wearing a plastic apron and gloves) are less expensive; estimated at ~£13.5-£14.5 per patient/day in the UK.[9] A course of vancomycin is approximately £530.

In the UK, an average increase in inpatient cost has been estimated as £4,798 (2007 prices) per MRSA case.[7] This is lower than studies reported in other countries; for example, in Canada, $CAN14,360 (£7,800, 2007 prices) [12]; in the USA, $US9,794 (£7,800) for bacteraemia [13] and $US13,901 (£12,000, 2007 prices) for post-surgical wound infections [14]; in France, $US9,275 (£7,400, 2007 prices) for ICU cases [15]; and in Israel for ICU patients, US$33,889 (£17,000, 2007 prices)[19]. Lower incremental costs are also reported for a teaching hospital in Spain, €2,730 (£2,100, 2007 prices).[41]

Using the UK figure of £4,798 per MRSA infection (2007/08 prices), combined with a figure of ~22,250 cases, the annual impact on **inpatient care costs is estimated at ~£106.75 million** in England (see **Table 2**). This excludes *ad hoc* government initiatives such as the £50 million scheme to "deep clean" every hospital in England. It also excludes the cost to the NHS of general infection control in hospitals, since this is difficult to apportion to particular HAIs.

MRSA decolonisation:
For NHS patients who are colonised with MRSA, decolonisation (comprising antibacterial shampoo and body wash and the application of an antibacterial nasal cream) is relatively inexpensive at £7.60 per patient (2008/09 prices). Since Trusts should now be screening all elective admissions [42], **annual decolonisation costs are estimated at ~£6.9 million** (allowing for false positives). By 2011, once emergency admissions are included, an **additional cost of £2.5 million** will be incurred for decolonisation.

3.2.3 MRSA: Cost of current testing

MRSA unit test costs:
Published unit test costs for individual tests specified in Section 2.1 are shown in **Table 3**. These figures only include consumable costs and should therefore be treated with considerable caution. One UK study has estimated full test costs, which include sampling, staff time, lab overheads etc. in addition to consumable costs.[9] For solid media (agar) the full unit cost is calculated to be £7.80 (for a positive test) and £5.06 (negative); and for broth enrichment it is £10.16 (positive) and £6.97 (negative). For real-time PCR (SmartCycler system with IDI MRSA Test Kit) the cost per sample was estimated to be ~£26.46 (negative and positive).

MRSA diagnostic testing costs:
In cases in where an infection is suspected, a diagnostic test will be requested. Assuming that one sample is tested from each patient and that ~20% of these are positive (see above), the cost per patient tested is estimated at ~£5.61 for agar and ~£7.61 for broth enrichment. Nationally, based on >22,250 MRSA infections (>111,250 patients tested if 20% of samples are positive), and the assumptions above, the cost of **diagnostic testing is estimated as ~£0.2 – £0.3 million per annum** in England.

MRSA screening programmes:
The NHS is committed to introducing MRSA screening for all elective admissions from 2008/09; and to extending this to cover all emergency admissions by no later than 2011.[43] The cost of screening will be significantly higher that the diagnostic test costs calculated above. The Department of Health has estimated that, in England, the cost of screening plus decolonisation over 10 years will total £1.22 billion.[42] Although several studies report that the benefits of MRSA screening are not yet proven [44-47], other papers suggest that implementing screening in conjunction with contact precautions can result in a significant reduction in MRSA cases.[48, 49]

For current screening tests, based on a single swab per patient and an assumed 7% prevalence rate [9, 26-29], use of a standard agar plating pre-admission test for 95% of electives and rapid PCR for the remainder (see cost figures above), an **annual screening cost of £68.4 million** is estimated for electives, as shown in **Table 2**. In 2011, once emergency admissions are included, assuming that

rapid PCR tests are used for all of these and standard agar for the rest, this figure will **increase to £181.88 million**.

For current screening (electives only), if all swabs are tested using PCR the annual screening cost rises to £290.4 million; if all were to be tested using standard agar it would fall to £57.8 million.

3.3 *C. difficile*: Economic disease burden & testing and treatment costs

Summary figures for the calculations below are presented in **Table 2**.

3.3.1 *C. difficile*: Economic burden of disease

Clostridium difficile infection (CDI) remains the main cause of hospital-acquired infectious diarrhoea, usually beginning following antibiotic exposure.[50-52] In terms of economic burden, CDI can impact on HRQoL and even be life-threatening, especially in elderly patients.[25] As well as exposure to antibiotics, other risk factors include a recent stay in a long-term care facility (e.g. nursing home) or hospital. After rising steadily, the number of CDI cases in patients aged 65 years and over decreased by 9% in 2007. This decrease should be interpreted with caution since it may not be sustained. [53]

C. difficile mortality:
In 2007, 4,056 death certificates in England and Wales reported CDI as the underlying cause of death and a further 4,268 mentioned it as a contributory cause.[21]. Once again, there appears to be considerable under-reporting with ~65% of deaths where CDI was a direct or probably cause not reported as such on death certificates.[22] This indicates that the 'true' number of deaths in 2007 with CDI as the underlying cause might be ~11,590. Considering all cases where CDI might have contributed to death, and allowing for under-reporting, this figure may actually be as high as ~23,780 deaths. Since only 22% of samples in 2007 were submitted from outside acute Trusts, it is likely that the majority of CDI deaths are linked to hospital infections.

The median age at death is not reported, although 82% of cases occur in the 65+ age group.[25] Comparative rates show ~3,400 deaths per million population in the 85+ age group, compared to ~0.7 deaths per million population in the under 45 age group in 2007.[21] Assuming a conservative 3 years lost per death, based on average UK life expectancy figures [23], we estimate ~12,168 Life Years (LYs) lost linked to the 4,056 deaths in England and Wales specifying CDI in 2007. This represents a total mortality cost of ~£330 million (assuming HRQoL of 0.7, life year valued as £38.8k). If this figure is adjusted for likely under-reporting, we estimate **a total mortality cost of ~£944 million** as shown in **Table 2**.

C. difficile morbidity:
The morbidity burden is linked to the total number of CDI cases. This was difficult to estimate while mandatory surveillance only covered cases in those aged 65 and over. In April 2007, this was extended to the 2-64 years age group, enabling the total number of infections to be estimated. In 2007/08, there were a total of 54,746 CDI cases reported for all ages in the UK. Just under half of these (24,168 cases, ~44%) were identified as hospital-acquired (detected 2+ days after admission); in a further 25% of cases (13,687) information was not available, giving a possible 37,850 cases of CDI. Only 22% of overall CDI cases originate from outside acute Trusts, which would suggest a maximum possible number of ~42,700 hospital cases in 2007/08.

It is not possible to estimate the number of QALYs lost through CDI due to lack of data on HRQoL. However, complications such as multiple CDI recurrences, intestinal perforation, sepsis and colectomy will clearly have a long-term impact on quality of life.[54] Also, new CDI strains are linked to increased disease severity, with 10% of these patients requiring colectomies, which will

impact on quality of life. Any trend of decreasing age for patients with CDI will also increase the QALY burden since any impact on HRQoL could extend over a greater number of years.

C. difficile costs to society:
No published UK studies provide an estimate of societal costs such as lost productivity/missed days of work resulting from CDI. The cost of CDI has been estimated as €3 billion/ year in the EU, equivalent to £400 million in a population the size of the UK; this figure appears low and may not include societal costs. [50] A similarly broad range has been reported by researchers in the USA, from $436 million to more than $3 billion societal costs. [55-57]

3.3.2 *C. difficile* : Cost of current treatment and control

For the calculations below, **Annex 1b** provides an overview of input parameters and assumptions used to estimate costs.

C. difficile inpatient care:
In the case of CDI, there is once again agreement that the main cost driver is the impact on hospital length of stay for the index episode, plus subsequent re-admissions to hospital.[58] Two UK studies have measured the incremental cost of CDI for hospital cases. A UK retrospective study calculated an average value of £3,000 per case at 2007/8 prices, with 93.8% of the additional cost linked to increased LOS. [59] A UK prospective study in a geriatric ward found a total cost difference of £4,107 (£5,600 at 2007 prices); 94% of the cost was due to increased LOS. [60]

Internationally, other studies have reported a difference of £6,750 (2007 prices) [61]; an increase in total hospital cost of $15,180 [62]; and a difference of €4,067-9,276. [63] A US study reports the largest incremental cost ($US22,600) for CDI in patients undergoing a major bowel procedure.[64] A large US 5 year retrospective analysis has shown that CDI is an independent predictor of increased LOS, total charges and mortality rates after surgery; total charges were found to increase by US$77,483 per patient.[65] For ICU patients, another study has reported a difference in cost of $US6,510.[66]

Assuming a conservative **incremental cost of ~£4,300 in the UK** (based on the £3,000 and £5,600 figures reported in the two UK studies above), CDI in 2007/08 is estimated to have increased **inpatient care costs by £183.6 million** for the index episode for ~42,700 hospital cases.

Re-admissions to hospital:
It is reported that approximately 20% - 27% of patients will have at least one CDI recurrence, with some patients experiencing as many as 14 episodes; recurrence rates for older patients (≥65 years) are reported to be particularly high, reaching 59.4% [67-69]. The additional cost associated with an index CDI episode will therefore not be limited to the inpatient stay in which infection occurred.

A retrospective analysis of hospital stay for patients admitted to hospital with recurrent CDI demonstrated a lifetime cost per patient approximately 3.5 times that of the initial episode.[70] A study in 19 Canadian hospitals estimates a similar cost increase for patients with re-admissions (average of 10 re-admissions).[71] These studies exclude the cost of complications, additional clinic visits, community care, and time lost from work, so the full healthcare cost increase is under estimated, as are associated societal costs.

Assuming that 20% of CDI cases in the UK (lower figure above) lead to recurrent episodes, and that the lifetime cost of care for such cases is 3.5 times higher, the estimated total national longer-term cost associated with CDI cases in 2007 will rise by 50% to **£202 million per annum** for 42,700 cases, to include subsequent re-admissions.

3.3.3 *C. difficile* : Cost of current testing

Our literature search was unable to identify any robust costing studies for the specific CDI tests mentioned in Section 2.1 (shown in **Table 3**). Absence of unit test cost figures which include staffing, capital and overheads is a major gap in the evidence base.

One UK study reported that the additional testing cost per CDI case was approximately £210 (£290 at 2007 prices). However, intensity of daily testing was largely similar for CDI and non-CDI cases, so that the cost difference was mainly linked to an increased LOS (equal to an average ~£9.85 per day). [60]

Assuming that 10% of hospital samples are positive for *C. difficile* toxins [72], 427,000 patients will be tested to identify ~42,700 cases. This equates to a **total testing cost of £4.3 million** at a unit test cost of £10. In the community setting, only 2% of samples are positive.

3.4 ESBL: Economic disease burden & testing and treatment costs

Summary figures for the calculations below are presented in **Table 2**.

3.4.1 ESBL: Economic burden of disease

A number of key risk factors for acquiring ESBLs have been identified as listed in Section 1 of the report. From an economic point of view, it is important that ESBL-producing bacteria are associated with increased morbidity as well as mortality [73]; and that patients with this infection require longer hospital stays than patients who are not infected with ESBL-producing strains.[74] Recent articles on paediatric ICUs, reporting similar ESBL prevalence to that observed in adults, are also important in terms of the potential length of impact on HRQoL.[75-80]

Although recent detection of ESBL producing *E. coli* associated with UTIs in the community are economically important [81-83], they are **outside the remit of the current economic assessment.** This trend may have important cost consequences if it leads to an increased need for parenteral antibiotics to treat UTI in the community. [82, 84]

ESBL mortality:
In the UK, the number of deaths each year in patients with infections caused by ESBL-producing bacteria is not known. It is therefore **not possible to accurately estimate ESBL mortality costs** for the UK.

Assuming that mortality is *principally* linked to blood stream infections, with a total of ~5,500 cases of ESBL *E. coli* bacteraemia in 2007 reported in the UK (excluding Scotland), and assuming a conservative mortality rate of ~5% - 10%, this would indicate ~275-550 deaths per annum (excluding Scotland) for *E. coli* infections. However, even this is likely to be a gross underestimate. Firstly, since it is based on voluntary reporting only.[74] Secondly, much higher mortality rates have been reported for patients with ESBL CTX-M with ESBL contributing directly to mortality in 19% of cases, and a contributing factor in a further 7.5%.[85] As a consequence, the number of ESBL-related deaths may be much higher.

Since an age profile for deaths involving ESBL-producers is not available, it is not possible to accurately estimate the number of Life Years lost or the associated mortality cost for ~275-550 deaths. Paediatric deaths will have greater economic consequences in terms of Life Years lost and associated mortality costs.[86] Assuming an average 10 years of life lost per person, this represents **a total mortality cost of ~£74.69 - £149.4 million** (assuming HRQoL of 0.7, life year valued as £38.8k) as shown in **Table 2**.

Finally, it is worth noting that it is still not universally accepted that ESBL infection is responsible for increased mortality.[87] Although a number of studies do report mortality rates, these vary in terms of whether they report crude mortality or mortality attributable to ESBL, and whether they include all ESBL-positive strains or focus on more virulent pathogens; they also almost exclusively focus on patients with bacteraemia. A recent meta-analysis examined reported impact on mortality for bacteraemia caused by *Enterobacteriaceae*.[88] The authors report a crude mortality of 20% among non-ESBL patients and 34% as the expected mortality among ESBL bacteraemia. However, these bacteraemia findings contrast with those from 8 other studies that included patients with other types of ESBL infection, where increased mortality was found in only one study. For intensive care units, a recent qualitative review of the literature concludes that ESBL-producing *Enterobacteriaceae* are generally associated with increased mortality in univariate analyses, although associations sometimes disappeared in multivariate analyses.[89]

However, there is consistent evidence that the main reason for mortality among patients with ESBL bacteraemia is a delay in initiating effective treatment.[90-92] A case-control study of inpatients with *E. coli*, *Klebsiellia* or *Proteus* bacteraemia found that patients with ESBL-positive strains were more likely to have a delay of > 48 hours to appropriate antibiotic therapy (66% versus 7%; $P< 0.001$).[93] In another prospective study of patients with *K. pneumoniae* at 12 hospitals in seven countries, failure to administer an appropriate antibiotic within the first 5 days resulted in significantly higher mortality than treatment with an appropriate antibiotic (63.6% versus 14.1%; $P= 0.001$).[94]

ESBL morbidity:
It is not possible to accurately estimate the morbidity burden associated with ESBL infection in UK hospitals. Comprehensive data on the annual number of infections are limited. For bacteraemia, the HPA has estimated ~2,000 infections due to ESBL *E. coli* in the UK (excluding Scotland).[95] Summing 2007 data for ESBL bacteraemia due to *E. coli*, *Klebsiella* and *Enterobacter* produces a figure of ~5,500 bloodstream infections.[85, 96] This data is based on voluntary reporting; it also excludes other infection sites (e.g. UTIs), so is likely to significantly underestimate the annual total number of ESBL-linked infections. Another source suggests a total of ~30,000 infections due to ESBL-producing *E. coli* alone each year in the UK.[95] Although the majority of ESBL cases are associated with UTIs, a significant minority of patients do have bacteraemia (40% in a review in the South East).[96]

Even if an accurate figure could be obtained for the annual number of ESBL infections, the QALY loss could not be estimated since the HRQoL of patients with ESBL infections has not been reported. The new severe strains (e.g. CTX-M) may have a greater impact on HRQoL. A number of studies report that delays in administering appropriate antibiotics contribute to increased morbidity, as well as mortality.[90-94]. Thus, there appears to be good evidence that the ESBL morbidity burden could be reduced through more rapid identification, but no quantitative data to allow this to be estimated.

ESBL costs to society:
There is no literature reporting the annual loss to the UK economy from ESBL infections.

3.4.2 ESBL: Cost of current treatment and control

Annex 1c provides an overview of input parameters and assumptions used to estimate costs below.

ESBL inpatient care:
As with other HAIs, the impact on hospital length of stay is reported to be the most important cost driver. However, to date the impact of ESBL infection on inpatient costs has been assessed in only a small number of studies.[97] Once again, separating the additional cost to the NHS from the underlying cost is difficult.

In the USA, patients with ESBL-producing *E. coli* or *K. pneumoniae* are reported to incur significantly greater hospital charges than matched controls (difference $44,359 per patient).[98] Even after controlling for APACHE II score and LOS before infection, infection with an ESBL-producing strain still nearly doubles charges. A more recent matched-cohort study of patients infected with ESBL-producing *E. coli* or *Klebsiella* at sites other than the urinary tract reported a difference of $16,451 per patient.[99] A third study of patients with *E. coli*, *Klebsiellia* spp. or *Proteus* spp has reported that ESBL-positive cases had a significantly higher average hospital cost (difference $30,093 per patient).[93] After adjusting for various potential confounding variables, ESBL still remained independently associated with increased hospital costs (P= 0.003).

Because there is no published UK economic study, we have assumed an incremental inpatient cost based on the lowest figure above ($16,451 or £8,225). Combining this with the estimated ~30,000 infections due to ESBL-producing *E. coli* alone, produces a conservative annual increase in **inpatient care costs of £246.75 million**

3.4.3 ESBL: Cost of current testing

Our search of the literature was unable to identify any robust published costing studies for the ESBL tests listed in Section 2.1 (and associated Table). This, together with the lack of data on numbers diagnosed and the prevalence of ESBL in samples tested, means that the **national cost of ESBL testing cannot currently be estimated**.

3.5 MRSA: Cost-effectiveness of individual tests & current testing

3.5.1 MRSA: Evidence on cost-effectiveness of testing

Our review of the literature identified relatively few studies reporting the cost-effectiveness of individual tests for diagnosing MRSA. Most recent papers focus on economic evaluation of screening for various types of hospital admission.

MRSA diagnostic testing:
For diagnostic samples, overall test effectiveness will depend not only on rapid antibiotic treatment for the patient diagnosed with MRSA infection, but also on introduction of control measures to limit transmission to other patients such as use of isolation rooms or cohorting. Expert opinion suggests that lapses in hand hygiene and aseptic practice would not, typically, represent more than 10% of cases.[42]

Section 2.1 (and associated Table) in the scientific report indicates that available MRSA tests are reported to have a range of sensitivity and specificity values. There is uncertainty over reported accuracy since papers do not generally meet accepted quality criteria, not least because there is no agreed reference standard for MRSA testing.[9] For modelling screening in Scotland, agar culture has been assumed to have a sensitivity of 68% (6% incidence of false-positives); broth enrichment culture a sensitivity of 98% (6% false-positives); and real-time PCR a sensitivity of 92% (9% false-positives).[9] An impact assessment by the Department of Health assumed tests had 90% sensitivity and 95% specificity.[42] If a test has a low sensitivity, risk to other patients will be increased as false negative MRSA patients may be managed in the open ward. If the test specificity is low (higher false positives) beds in isolation facilities may be occupied unnecessarily.

Table 3a demonstrates the broad range of costs reported for tests listed in Section 2.1. However, since there is no reliable data to confirm which tests are most widely used in the UK (i.e. market share) it is difficult to draw conclusions about overall cost-effectiveness in the NHS. Furthermore,

there is uncertainty over the effectiveness of control measures which may be used following a positive test result, especially the independent effects of one measure in comparison with another.[100]

MRSA Screening programmes:
There is more evidence on the cost-effectiveness of MRSA screening tests. Tests will inevitably misclassify some patients as screen positive or negative in the same way as screening tests for other infectious disease.[101] The effectiveness of any screening programme will also depend on the efficacy of decolonisation and any associated interventions (e.g. isolation/cohorting) as well as the risk for a particular patient group. The impact of MRSA infection can be particularly serious in certain specialties.[102] Infections may still occur in patients who are known to be colonised with MRSA and for whom decolonisation treatment is ineffective. Decolonisation is reported to be only 50-60% effective for long-term clearance [103].

A number of recent articles (2006-08) provide mixed evidence on the economics of MRSA screening, with findings generally presented in the form of a 'cost analysis'. Cost-utility analyses (i.e. cost/ QALY) are absent. Several studies report that screening is cost-effective, although the cost-effectiveness of rapid PCR testing is questioned in three studies.

- A study in a teaching hospital in Spain has estimated that the cost of a programme would be covered if it prevents 4 infections per year (11% of total infections).[41] A similar study in Germany has estimated that €20,000 could be saved by detecting and successfully decolonising a total of five patients through pre-admission screening in general surgery.[104]

- In the USA, the cost-effectiveness of screening all patients admitted to medical and surgical and intensive care units for MRSA nasal carriage has been assessed over a 15 month period. The authors report an estimated $US19,714 saving per month through averted MRSA infections.[105] Rapid pre-admission testing for US patients undergoing elective surgery is predicted to produce a mean annual hospital cost saving of $US231,538,400 in another study.[106] Rapid PCR testing of hospital readmissions among previous MRSA carriers is reported to reduce isolation days by 54% and reduce costs from $US113.2 to $US62.1.[107]

- In Switzerland, a cohort study has evaluated rapid molecular MRSA screening in ICU. This was observed to substantially reduced MRSA cross-infections in the medical but not in the surgical ICU.[108] Another Swiss study reports that use of PCR for contact screening for MRSA carriage increased costs by 104,328 Swiss francs (CHF) but only saved CHF 38,528 for pre-emptive isolation. It is concluded that, in patient populations with low endemic MRSA, the use of PCR is probably not cost-effective.[109]

- In Germany, a hospital-wide screening programme was judged to prevent 48% of predicted hospital-acquired MRSA infections resulting in a net annual saving of €110,237.[40]

- In France, a cluster randomised trial has examined whether rapid testing reduces MRSA acquisition. No evidence was found of a significant reduction in MRSA acquisition and it was concluded that it is unlikely that the increased costs of rapid tests can be justified, compared with alternative control measures against MRSA.[47]

- A Canadian decision analysis compared the costs of detection by PCR and by culture. Cost per patient was higher for detection by PCR ($CAN96) than by culture ($CAN67). Overall costs increased from $CAN605,034 to $CAN771,609, with 37% of the increase due to

patients being placed under contact precautions unnecessarily due to low specificity of the PCR test.[110]

- Three other studies have concluded that the clinical benefits of screening are not proven, although economic analyses are not included.[44-46]

In the UK, it is estimated that although screening would cost the NHS £1.22 billion over 10 years in England, it would actually result in cash saving in treatment costs of MRSA bacteraemia and wound infections of £1.19 billion.[42] This calculation assumes that all elective admissions will receive a pre-admission test (standard agar), and that emergencies will be screened using a rapid PCR test. Economic modelling in Scotland suggests that real-time PCR is unlikely to replace culture for blanket MRSA screening of patients, primarily because test accuracy is lower than for enrichment broth.[9] This view is not supported by other authors who suggest that there may be a role for PCR on specific wards, where the risk of colonisation or infection is high and preadmission screening is not possible.[111] The economic viability of screening will depends primarily on the relationship between colonisation and infection risk. Decolonisation costs are relatively small, whilst benefits (including lives saved) will depend on the likelihood of a serious MRSA infection resulting from a colonised patient. In the UK, it has been estimated that if risk falls to around 1 case per 700 colonised patients, the economic calculation becomes neutral.[42]

3.6 *C. difficile*: Cost-effectiveness of individual tests & current testing

3.6.1 *C. difficile*: Evidence on cost-effectiveness of testing

There is very little published on the cost-effectiveness of existing tests for CDI. Considering the high costs associated with CDI morbidity and death, this represents a major research gap. The most cost-effective approach to identification will be determined by the clinical context, any recognisable causes, and the cost and yield of available diagnostic tests.

If a test has a low sensitivity (producing false negatives), patients will not receive appropriate treatment. This will lead to more serious illness for patients themselves and increased risk to other patients since the infected patients will not be isolated and instead managed in the open ward. Each resulting transmission could lead to ~£4,300 in additional healthcare costs; more with high risk patients e.g. in ITU. If test specificity is low (producing false positives) antibiotic treatment for other conditions may be stopped and patients treated inappropriately for CDI. Beds in high cost isolation facilities may also be occupied unnecessarily and if the patient is nursed with other true CDI cases, there will be a risk of infection. Once the infection is diagnosed, testing costs (£210) represent only a small fraction of overall inpatient CDI care costs.[60]

CDI diagnostic testing:
As speed of diagnosis is important for the efficient use of isolation facilities, clinicians need to ensure that faecal specimens are sent for testing as soon as infective diarrhoea is suspected.[22] Tests detecting toxins are considered to be more cost-effective.[112]

There are now more than a dozen commercial antibody-based tests for *C. difficile* on the market. Although these tests may be perceived as cost-effective, any incorrect results will add to the cost of care (see above). A meta-analysis reporting on 6 toxin detection kits found that PPV is generally poor (less than 50% in some cases).[113] The fact that many laboratories have introduced these kits is likely to have increased the number of incorrect results.

The use of these kits to diagnose *C. difficile* has been questioned recently, especially in the context of widespread testing.[114] However, an economic analysis of the cost-effectiveness of toxin

detection kits has not been undertaken in the NHS. If the first test from a patient is negative, experts recommend that a second test be performed to definitely rule-out disease.

CDI screening strategies:
Because most samples tested for CDI are negative (90% of hospital samples and 98% of community ones [72]), an efficient, rapid screening test could not only reduce turn-around time for reporting negative results but also decrease overall costs. A number of authors provide assessments of different screening strategies.[115, 116] These include a two-step algorithm with a first stage (antigen test) followed by a culture cytotoxin assay for positive specimens [117, 118]; or a rapid screen by an immunoassay followed by toxin testing for screen-positive specimens, and stool culture for toxin-negative specimens. [119] Such approaches are reported to offer laboratories a simpler, faster, and more cost-effective testing protocol for *C. difficile*, as well as reducing workload. Although step-testing is reported to be cost-effective, the authors present no figures to support this statement.

3.7 ESBL: Cost-effectiveness of individual tests & current testing

The rising importance of ESBL-producing organisms necessitates effective screening methods for their detection. A testing strategy for ESBL will include an initial screen using an indicator drug e.g. cephalosporin to identify likely producers, followed by a confirmatory test for screen-positive isolates.[120] Different tests are available to help confirm ESBL susceptibility, including combination disc methods or the more expensive Etest ESBL strips. [121] Alternatively, a single-test can be used (e.g. Vitek test). A recent review of articles (1966-May 2007) evaluating laboratory methods for detection of ESBLs (and AmpC beta-lactamases) identified numerous laboratory techniques available for detection of ESBLs.[122] However, the authors conclude that tests currently recommended can be associated with both false negative and false positive results. In particular, routine microbiologic testing may not detect ESBLs because in vitro susceptibility does not always correlate with clinical outcomes. This may influence the utilisation of test results by clinicians.

3.7.1 ESBL: Evidence on cost-effectiveness of testing

Our review of the literature has identified very few studies reporting the cost-effectiveness of tests for diagnosing ESBL. Several papers indicate that strategies currently used for patients with ESBL bacteraemia are inefficient and need to be revised. A three pronged approach has been suggested to include facilitating diagnosis and reporting of ESBL production, revising empirical therapy choices, and improving definitive treatment.[93]

The few studies which allegedly describe the economic impact of new detection methods for ESBLs are simplistic and usually do not go further than stating that a method is simple, rapid and low-cost.[123] One recent study concentrated on how test information is used and found that the majority of clinicians acted on a positive laboratory result; with 40% changing to appropriate monotherapy and another 23% substituting for an inactive antibiotic.[124] A second study investigated clinician response to ESBL confirmation reports for *E. coli* or *Klebsiella* species non-urinary infection generated by an automated detection system (MicroScan Walkaway); acceptance was observed in 69.2 % of the post-automated detection cohort versus 20 % in the pre-automated detection period ($P \leq 0.001$).[125] Although there was earlier initiation of appropriate therapy, reductions in length of stay and mortality were not observed.

Another paper on detection of *Klebsiella* pneumoniae-produced ESBL in a hospital with high prevalence reports that the E-test demonstrated higher accuracy but was more expensive than the disk diffusion method.[126] An economic review has been undertaken of this paper [127] Total costs for each diagnostic strategy were estimated for different ESBL prevalence. For the E-test, at

ESBL prevalence of 2% the total cost is $37,260, and at 10%, the cost is $48,332. For the disk diffusion method, the cost is $44,484 at 2% prevalence, and $55,556 at 10% prevalence. The lower prevalence figure may be more appropriate for the NHS. Screening of diarrhoea samples in one UK hospital has shown faecal carriage of ESBL-positive *E. coli* in 4.6% of acute hospital in-patients. [96]

3.8 Estimating the economic benefits which new tests could provide

3.8.1 Overview of economic analysis and model used

Current testing scenarios (Tables 4a-c):
Tables 4a - 4c present an overview of the UK status quo for MRSA, CDI and ESBL testing respectively. Comparative data are provided for the technical performance (sensitivity/specificity) of tests currently used; times to result; and the location of testing. The numbers of inpatients being tested annually is also presented (where this can be estimated). For MRSA (**Table 4a**) tests where an infection is suspected are distinguished from population screening tests. For ESBL, the annual number of tests could not be estimated with any accuracy.

The final two columns in **Tables 4a-c** summarise the economic impact of each infection in UK hospitals, as detailed in sections 3.2 - 3.4 above. Annex 1 provides an overview of input parameters and assumptions used to estimate these costs.

In **Table 4a**, the annual burden of disease for MRSA hospital infections includes costs associated with mortality together with incremental inpatient costs. Morbidity costs are excluded (unavailable). NHS costs incurred after discharge (GP consultations and community nurse visits) are also excluded; as are societal costs such as lost productivity/missed days of work.

The penultimate column provides an estimate of current national expenditure on MRSA testing. For MRSA screening tests, two extreme testing scenarios are presented – one in which PCR tests only are used (maximum cost) and one using culture tests only (minimum cost). NHS policy guidance does not specify which tests should be used for screening.

Table 4b presents similar economic information in the final two columns for C. *difficile* hospital infections. These indicate that CDI is associated with a higher economic burden than MRSA. In contrast, annual testing costs are higher for MRSA because of the significant volume of screening tests. For CDI, total testing costs are much smaller (~£4.3 million).

It was not possible to estimate the current market for ESBL tests.

Tables 4c provides estimates of the burden of disease for ESBL infections (although figures are highly speculative)

New testing scenarios (Tables 5a-c):
Tables 5a - 5c present the characteristics of an 'ideal' new test for detecting these 3 infections. The Tables include information on test requirements (sensitivity/ specificity, time to result, and test process/setting) for the new test.

An economic model has been constructed to estimate the predicted economic benefits at national level of moving from the current status quo to implementation of one of the new tests.

The economic model:
A relatively simple economic model was constructed in Excel to estimate the costs of diagnosis and treatment (including isolation/ cohorting) of the three infections (MRSA, C. *difficile* and ESBL), and longer terms consequences such as mortality. These were compared for different tests (status quo and new)

In our analysis we focused on estimating incremental direct cost on moving from current testing to the proposed new test at year 1. Based on different parameter assumptions, the model then estimated the total cost and the number of infections detected. In the time available it was not possible to develop a more sophisticated model (e.g. simulation) which would be able to show national level costs and benefits over an extended time period.

Data in the model:
The model parameters were based on the highest level of evidence available from our review of the literature, and through contacting experts.

The main economic drivers for the new diagnostic tests were assumed to be changes in the number of false negatives/false positives and increases in the number of true positives detected. These in their turn were assumed to impact on the number of infections transmitted and on mortality.

The impact on morbidity could not quantified due to lack of robust data (e.g. QALYs), and was not included in the model for any of the 3 infections.

For MRSA, the reduced turn-around time for a diagnostic result (from 48 hrs for culture to 20 min for new Point of Care (PoC) test) was included in the model. It was assumed that transmission of infection would fall to ~zero with the new PoC test. The model was run for varying numbers of annual diagnostic tests (111,250 – 500,000) and for different infection transmission rates (0.3 – 0.7).

In the case of CDI diagnosis, the difference turn-around time was much smaller (3 hrs for ELISA to 20 min for new PoC). This, combined with a lack of robust transmission rate data, meant that we made no attempt to estimate the impact of reduced turn-around-time in this case. The model was run for an assumed 427,000 annual diagnostic tests, and for varying infection transmission rates (0.3 – 0.7).

For diagnosis of ESBL, most data items were missing. It was not possible to estimate values for the main parameters required to model economic benefits. Therefore, no attempt was made to quantify the economic benefits of a new PoC test (see **Table 5c**). This would require a separate data collection exercise.

For MRSA screening tests, the model computed additional true positive cases detected (see **Table 6a (ii)**). However, the monetary value placed on these could not be estimated. This will be dependent on factors for which definitive data was not available; these include the likelihood of an individual moving from a colonised to infected state if colonisation undetected, the rate of colonisation transmission to other patients during the hospital stay, and the effectiveness of decolonisation treatment. In our simple model, there was therefore no attempt to go beyond quantifying the extra colonised cases detected. The model was run for 15.7 million screening tests (all electives and emergency admission), and for different infection transmission rates (0.3 – 0.7).

Costs:
For each testing scenario, we estimated the number of cases of detected/ undetected and treated/ untreated infections and subsequent direct cost consequences. Indirect and intangible costs associated with these infections, including lost time from work, pain, anxiety, and long-term morbidity were not included in the analysis. Thus, the results presented below are likely to be an underestimate.

Results for MRSA:

Table 6a (i) shows that changing to a new test with improved sensitivity but decreased specificity (**Table 4a** status quo versus new test **Table 5a**) does not necessarily guarantee national savings when screening and diagnostic tests are considered together. Savings will be dependent on which tests are currently used for screening, the number of suspected cases tested (diagnostic tests), and the assumed infection transmission rate. The Table shows that, when the new test is compared to culture screening in a sensitivity analysis, an **annual cost saving** of £1.8 to £150 million (depending on infection transmission rate) is predicted if the **new test unit cost** is **similar to culture tests**, and assuming ~111,000 tests per annum for suspected infection (diagnostic). In this scenario, increased costs due to treatment of more cases will be compensated for by fewer infections transmitted (and a decrease in associated mortality and inpatient stay costs). If the number of diagnostic tests rises to half a million, the savings increase significantly. Under a scenario in which the unit test cost is **similar to PCR tests**, although more cases will be detected, there will be **no national cost saving** at lower diagnostic test numbers, and for higher numbers the Table shows savings will only occur at the higher transmission rate.

Table 6a (ii) indicates that if the new test were to replace **diagnostic** MRSA culture tests, **significant cost savings** can also be achieved, especially if transmission rates are high (see **Figure 1a**).

For screening, **Table 6a (iii)** shows the numbers of true and false positives, plus the number of false negatives, if different tests are used for screening. The estimated number of extra patients colonised due to the 48 hours turn-around time when culture is used as an admission screen is also included. The annual cost of decolonisation is presented for all 3 scenarios.

Results for CDI:

The costs and financial benefits of the two scenarios (**Table 4b** status quo versus new test **Table 5b**) were similarly modelled. Here the new test will result in improved sensitivity (more cases detected, model not actual) and a more rapid test result. Two levels of improvement in test parameters were modelled, based on Elisa vs Assay sensitivity/ specificity values and Elisa vs Culture values. In both cases, the additional cases detected will lead to extra treatment costs (which are relatively low), but will result in fewer infections transmitted and lower inpatient and mortality costs (which are relatively high). **Table 6b** shows that for 427,000 patients tested per annum there will be an **annual cost saving** at higher transmission rates, but not at the lowest transmission rate (see also **Figure 1b**).

For CDI, an estimate of the break-even cost for the new test can also be estimated at £49 - £173 (see **Table 5b**). These figures are based on the sum of current total spend on testing plus the predicted savings resulting from improved performance of the new test, divided by the number of tests to be performed. Two sets of figures are provided based on ELISA versus Culture sensitivity/specificity values, and on ELISA versus Assay data.

A similar break-even cost figure could not be estimated for MRSA because of the number of scenarios considered and the associated range of parameters.

Results for ESBL:

Costs could not be modeled for ESBL due to a lack of robust data on key parameters.

Extra cases detected:
For each testing scenario and type of infection, we estimated the number of additional cases which would be detected following introduction of the new PoC test. **Table 5a** shows the

extra number of MRSA cases (excludes colonisations) and **Table 5b** the extra number of CDIs. Figures could not be estimated for ESBL (**Table 5c**).

3.8.2 Economic conclusions

For MRSA diagnosis, **Table 6a (ii)** shows that a new PoC test could be highly money-saving. **Table 6a (i)** indicates that overall savings for diagnosis and screening will be dependent on the unit test cost of the new PoC test (for both minimum and maximum number of diagnostic tests performed). If the PoC test can only be offered at current PCR prices, then overall the new test will only be money saving the higher number of diagnostic tests is performed, and transmission rates are high.

Assuming a unit test cost equal to current culture tests, at the lower diagnostic testing level (111,250 per annum) **Table 6a (i)** shows that the annual financial benefit predicted with the new test is a saving of £1.8 - £149.8 million. At higher diagnostic testing levels (500,000) this figure rises to a maximum of £914.0 million (depending on the assumed transmission rate).

Table 6a (ii) also shows that under all scenarios, moving to the new test would detect additional MRSA infections; 5,118 annually for the lower diagnostic testing level and 23,000 for the higher.

For diagnosis of CDI, **Table 6b** illustrates that a new PoC test can also be money-saving, but only at higher transmission rates ($\geq$0.33). The Table demonstrates that moving to the new test would once again detect additional cases; 7,686 if the PoC test replaces culture and 4,270 if replacing Assay.

All the economic benefits above have been modelled based primarily on change in test sensitivity and specificity. The fact that the new test offers a shorter turn-around time has also been included for MRSA testing.

In conclusion, due to the limited time available for this complex modelling exercise, the findings should be treated with some caution. It has not been possible to develop a simulation model which would demonstrate economic benefits at a national level over time following implementation of the new PoC tests. We recommend that this be considered for both MRSA and C. *difficile*. In the event that more detailed specifications for the two new tests can be provided (what equipment will be needed, the type (and cost) of test kits, the level of staff required to perform the tests, whether a human reader is required etc.), it should be possible to better indicate relative savings linked to the new tests.

HAIs: TABLES

TABLE 2: HAIs Economic Impact in the UK (2007)

	MRSA	C Diff	ESBL
UK DISEASE BURDEN			
MORBIDITY			
Annual number of cases	>22,250[2]	42,700	~30,000[8]
Morbidity: Annual QALYs lost	N/A	N/A	N/A
MORTALITY			
Annual number of deaths[1]	460[3] [1,314]	4,056[3] [11,590]	~275-550
Av. age at death	~85 yrs	~76	N/A
Life Years (LYs) lost	2,560[3] [7,313]	12,168 [34,770]	N/A
Monetary value of LYs lost	**~£69 m[3] [~£198 m]**	**~£330 m[3] [~£944]**	**~£74.7-£149.4m[9]**
UK SOCIETAL COSTS			
Annual total cost to economy	**£3-11 billion[4]**	***£400 million***	**N/A**
NHS CARE/TREATMENT COSTS			
Annual drug therapy costs	£6.9 m[5]	*Included below*	*Included below*
Annual hospital care costs	>£106.75 m	£202 m	~£246.8[8]
Total annual treatment cost	**>£113.65 m**	**£202 m[7]**	**~£246.8[8]**
INCREMENTAL HOSPITAL COST/CASE			
Added cost/case	£4,798[6]	~£4,300 [£6,450] [7]	~£8,225

[1] England & Wales, 2007 figures
[2] England, 2007/08 estimated total figure for bacteraemia & wound infections.
[3] Deaths where infection is underlying cause [bracket: adjusted for under-reporting]
[4] Includes productivity loss/sick benefit
[5] Includes current decolonisation costs (based on all elective admissions screened)
[6] 2007/08 prices
[7] Higher figure includes estimated cost of CDI recurrence in 20%.
[8] Figure based on ESBL-producing *E. coli* cases only.
[9] Assumes an average 10 years of life lost per person.

TABLE 3: HAIs Unit Test Costs *(Converted to 2007 prices)*

Test name	Cost/test (£) (consumables only)	Source(s)
MRSA tests		
BBL™ CHROMagar™ MRSA	2.3 0.86	[129] [130]
Brilliance™ MRSA Agar	0.55	www.supplychain.nhs.uk
ChromID	0.55	www.supplychain.nhs.uk
Staphychrom II	N/A	
MRSA ID	0.76	[130]
Mannitol salt agar with oxacillin (OMSA)	N/A	
MRSA Select(R)	0.47 0.63	www.supplychain.nhs.uk [130]
ORSAB Select Medium	N/A	
MANNITOL SALT BROTH	1.19	www.supplychain.nhs.uk
PBP2′ latex agglutination test	11.6$kit	http://www.fishersci.com/wps/portal/PRODUCTDETAIL?href=&aid=112906
Screen Latex Agglutination Test	N/A	No published source
Staphaurex® Plus	6.63$	[131]
GeneOhm StaphSR	15.7	www.supplychain.nhs.uk
BD GeneOhm™ MRSA Assay	14.5	www.supplychain.nhs.uk
GenoQuick MRSA	10.39	www.supplychain.nhs.uk
GenoType MRSA	23.52	[130]
LightCycler	N/A	No published source
ReaX PCR	25.50$	
VirEp	N/A	No published source
Evigene Kit	N/A	No published source
Xpert™ MRSA	26.40	www.supplychain.nhs.uk
Velox	N/A	No published source
BacLite Rapid MRSA	*No longer used*	
CAMBR Biosensor	N/A	No published source
***C. difficile* tests**		
BBL Media	N/A	No published source
Brazier CCEY Agar - Cycloserine-cefoxitin-egg yolk agar	N/A	No published source
C. *difficile* Agar Base and Supplement	N/A	No published source
Clostridium difficile agar	N/A	No published source
Cycloserine-cefoxitin-fructose agar	N/A	No published source
BD ColorPAC Toxin A test	N/A	No published source
Premier Immunocard *C difficile*	N/A	No published source
Remel Xpect	N/A	No published source
Tox A/B Quik Chek	N/A	No published source
Triage C diff panel	N/A	No published source
C difficile Toxin A+B	N/A	No published source
C. DIFF CHEK™-30	N/A	No published source
GA Clostridium difficile Antigen	N/A	No published source
Premier Toxin A+B	N/A	No published source
Remel ProSpecT	N/A	No published source
Ridascreen toxin A/B	N/A	No published source
Toxin A/B II	N/A	No published source
Vidas C. difficile Toxin A &B	N/A	No published source
C. DIFF QUIK CHEK™,	N/A	No published source
CDT	N/A	No published source

Test name	Cost/test (£) (consumables only)	Source(s)
ESBL tests		
PHOENIX	N/A	No published source
VITEK	N/A	No published source
Cica B test	N/A	No published source
MicroScan ESBL plus panel	N/A	No published source
chromID ESBL	N/A	No published source
Chromagar CTX	N/A	No published source
Chromagar ECC	N/A	No published source
BLSE agar	N/A	No published source
E-test (Ceftazidime +/- clavulanic acid)	N/A	No published source
E-test (Cefotaxime +/- clavulanic acid)	N/A	No published source
Antibiotic discs (Cloxacillin and boric acid)	N/A	No published source
Antibiotic discs (Cefpodoxime/clavulante)	N/A	No published source

TABLE 4a: Overview and summary of current testing for MRSA (2009 scenario)

Clinical context for diagnosis	Current UK test context		Current tests used			Current test capability		Current economic impact	
	Number of UK patients tested annually	Settings where tests undertaken	Type of tests used	Test process	Type of specimen	Time to perform test/result	Sensitivity/ Specificity	Annual Testing Cost[2]	Annual Burden of disease
MRSA screening	~11 million[1]	Laboratory	Culture detection using Chromagar	Culture, followed by confirmatory tests	Nasal, groin, axilla, wounds, urine	48h	Mean: Sens 72% Spec 97%	£57.8 – £290.4 million [£68.4 million[4]]	Mortality: £198 million[3] IP cost (incremental): £106.75 million Decolonisation: £6.9 million
	~11 million[1]	*Laboratory*	*Molecular methods (BD PCR)*	*One step molecular tests*	*Nasal samples*	*2h*	*Sens 91% Spec 96%*		
MRSA clinical diagnosis	111,250 - 500,000	Laboratory	Culture detection	Culture followed by confirmatory tests	Wound, Blood	48h	Mean: Sens 72% Spec 97%	£0.2 - £0.3 million	
								Total: ~£69[4] million	**Total: £311.65 million**
								GRAND TOTAL = ~£381 million	

[1] Assumes only elective admissions are screening at present.

[2] MRSA screening: higher figure assumes PCR is only test used; lower figure assumes only culture is used.
MRSA clinical diagnostic: higher figure assumes 500,000 patients tested for suspected MRSA, lower figure assumes 111,250.

[3] Includes allowance for under-reporting of deaths.

[4] Assuming screening uses standard agar plating pre-admission test for 95% of electives and rapid PCR for the remainder.

TABLE 4b: Overview and summary of current testing for *C. difficile*

Clinical context for diagnosis	Current UK test context		Current tests used			Current test capability		Current economic impact	
	Number of UK patients tested annually	Settings where tests undertaken	Type of tests used	Test process	Type of specimen	Time to perform test/result	Sensitivity/ Specificity	Annual Testing Cost	Annual Burden of disease
C difficile clinical diagnosis	427,000	Laboratory	ELISA	One step test	Faeces	3h	Mean†: Sens vs Culture 77% Spec vs Culture 95% Sens vs Assay 85% Spec vs Assay 95%	£4.3 million	Mortality: £944 m[1] IP cost (incremental): £202 m **Total: £1,146 million**
								GRAND TOTAL = £1,150.3 million	

† Calculated for 7 ELISAs: C. DIFF CHEK™-30, GA Clostridium difficile Antigen, Premier Toxin A+B, Remel ProSpecT, Ridascreen toxin A/B, Toxin A/B II, Vidas C. difficile Toxin A &B

[1] Includes allowance for under-reporting of deaths.

TABLE 4c: Overview and summary of current testing for ESBL

Clinical context for diagnosis	Current UK test context		Current tests used			Current test capability		Current economic impact	
	Number of UK patients tested annually	Settings where tests undertaken	Type of tests used	Test process	Type of specimen	Time to perform test/result	Sensitivity/ Specificity	Annual Testing Cost	Annual Burden of disease
ESBL clinical diagnosis	N/A	Laboratory	Culture	Culture followed by confirmatory tests	Swab, Urine	48h	Mean‡: Sens 93% Spec 54%	N/A	Mortality: £74.7 - £149.4 m IP cost (incremental): ~£247 m **Total: £322 - £396 million**
								GRAND TOTAL = > £322 million	

‡ Calculated for chromID ESBL, Chromagar CTX, Chromagar ECC, BLSE agar

TABLE 5a: Predicted likely economic benefits of new tests for MRSA

	Main driver(s) for technology development	New test UK role	Target population/ sub-population		Ideal new test requirement				Predicted economics of new test			Main driver for technology implementation
			Target population to be tested	Number of UK patients	Time to result	Sens / Spec	Setting for test	Test process	Break-even Test Cost[2]	Annual Cost saving	Extra Cases[4] Detected per Annum	
MRSA	Screening with selective agar slow and chromogenic media has a low sensitivity in less than 48 h. Molecular testing requires high volume and is expensive.	Detection and screening	Hospital Community[1]	Screen: 15.7 million Diag: 111,250 – 500,000	20 mins	95/95	Point of care	Swab – nasal/rectal / wound "Dipstick" Single step	N/A	£1.8 - £914 million[3]	5,118-23,000	Ability to detect MRSA at the bedside to eliminate the need for transporting of specimens[5] and to enable medical staff to act on results immediately.

[1] Modelling economic benefits for community infections would require separate exercise.
[2] Break-even cost not available; will depend on assumed number of diagnostic tests (111,25- - 500,000), and infection transmission rate (range 0.3 to 0.7).
[3] Based on reduced mortality costs and hospital costs associated with improved test performance (fewer false negatives/ false positives etc). Figures are for varying diagnostic test numbers, new test price and transmission rates (See Table 6a(i) for more detailed analysis)
[4] MRSA infections only, excludes extra colonised patients detected.
[5] Marginal cost saving through avoidance of in-hospital specimen transport to laboratory will be small; balanced against this, there may be extra bedside quality control measures required.

TABLE 5b: Predicted likely economic benefits of new tests for *C. difficile*

	Main driver(s) for technology development	New test UK role	Target population/ sub-population		Ideal new test requirement				Predicted economics of new test			Main driver for technology implementation
			Target population to be tested	Number of UK patients	Time to result	Sens / Spec	Setting for test	Test process	Break-even Test Cost[2]	Annual Cost Saving[3]	Extra Cases Detected per Annum	
C. difficile	ELISA tests are the main test currently in use for the detection of toxin A and B but they lack specificity, sensitivity and have low PPV. All testing takes place within the laboratory and a stool sample is required	Detection of disease	Hospital Care Homes[1]	427,000	20 mins	95/95	Bedside	Blood Stool sample toxin detection Single step. Portable device	£48.7 - £100.5 *[£79.9 - £172.8]*	£16.5-£38.6 million[4] [£29.8-£69.5 million][5]	4,270-7,686	A bedside test will enable patients with diarrhoea to be isolated promptly and therefore limit the spread of the organism which has an ability to survive for extended periods within the environment.

[1] Value of parameters required to model economic benefits for care home infections not available; would require separate data collection exercise.
[2] Ratio of: (Current total spend on diagnosis + predicted savings due to improved test performance)/ Number of tests performed, 0.427 million) for Elisa vs Assay sens/spec values Table 4b. [*Brackets: Same ratio based on Elisa vs Culture sens/spec values*]
[3] Based on reduced mortality costs and hospital costs associated with improved test performance (fewer false negatives/ false positives etc)
[4] Based on current test characteristics (Elisa) vs Assay
[5] Based on current test characteristics (Elisa) vs Culture

TABLE 5c: Predicted likely economic benefits of new tests for ESBL

	Main driver(s) for technology development	New test UK role	Target population/ sub-population		Ideal new test requirement				Predicted economics of new test [1]			Main driver for technology implementation
			Target population to be tested	Number of UK patients	Time to result	Sens / Spec	Setting for test	Test process	Break-even Test Cost	Annual Cost Saving	Extra Cases Detected	
ESBLs	Currently screening tests are not specific as other mechanisms than ESBLs may cause positive screens. Currently different methods depending organism. Development of new enzymes. Current methods take greater than 48h to result.	Detection	Hospital Community	N/A	< 30 mins	95/> 95	Laboratory Point of care	"Dipstick" for urines Laboratory (single step)	N/A	N/A	N/A	Rising numbers of ESBLs (particularly in community UTIs) justify development of community rapid test[2].

[1] Value of parameters required to model economic benefits not available; would require separate data collection exercise.
[2] Community infections excluded from Annual Burden of Disease estimates (see Table 4c).

TABLE 6a: Sensitivity analysis MRSA

(i) New Test Replaces Current Tests for Screening & Diagnosis

Annual savings: New MRSA test used for screening all cases & diagnosis for max/ min number of patients tested

No. UK patients with suspected MRSA (Diagnostic tests)[1]	Total Annual UK Cost (Screening[1] + Diagnosis)			
	Current tests[3]		New POC test[4]	
	Culture screen	*PCR Screen*	*New POC test (screen & diagnostic) Unit test cost = Culture cost*	*New POC test (screen & diagnostic) Unit test cost = PCR cost*
111,250	£83.2 m	£415.9 m	- £1.8 to - £149.8 m[5]	+ £182.9 to + £330.0 m[6]
500,000	£86 m	£418.7 m	- £296 to - £914 m[5]	- £581.0 m[5] to + £414.2 m[6]

[1] Assumes all electives & emergencies are screened (~15.7 million patients)

[2] Rows assume varying number suspected cases undergo diagnostic tests (111,250 – 500,000)

[3] Assumes all patients are screened using same test: either using only culture or only PCR test.

[4] Cost range in cell based on possible variation in infection transmission rate (0.3 to 0.7)

[5] -£ = Saving compared to current tests

[6] +£ = Increased cost compared to current tests

(ii) New Test Replaces Current Tests for Diagnosis

Annual savings: New MRSA test (compared to current test) for different transmission rates & numbers tested

Numbers Tested	Transmission rate (false negatives & true positives[1])	Annual Savings (compared to current test)	Extra cases detected (per annum)
111,250	0.3	- £ 85.0 m	5,118
	0.5	- £ 159.0 m	
	0.7	- £ 233.0 m	
500,000	0.3	- £ 382.0 m	23,000
	0.5	- £ 714.0 m	
	0.7	- £1,000.0 m	

[1] True positives (MRSA infection) take 48 hr to be detected using culture methods; during this time they are assumed to transmit infection at this rate.

(iii) MRSA Screening: Types of Results, Decolonisation Costs and Extra Colonisations for Different Screening Tests (15.7 million)

	Type of test used for screening on admission		
Annual Results	**Culture**	**PCR**	**New PoC**
No. True Positives	791,280	1,000,090	1,044,050
No. False Positives	438,030	585,040	730,050
No. False Negatives	307,720	98,910	54,950
Annual Cost			
Decolonisation Cost	£9.3 million	£12.0 million	£13.5 million
Extra colonisations			
Time to result	48 hrs	2 hrs	20 mins
Transmission	0.3	0	0
Extra patients colonised	329,700	0	0

TABLE 6b: Sensitivity analysis C. *difficile* (New Test Replaces Current Test for Diagnosis)

Annual savings: New C. *difficile* test (compared to current test) for different transmission rates

Numbers Tested	Transmission rate per false negative	Elisa vs. Culture	Extra cases detected (per annum)	Elisa vs. Assay	Extra cases detected (per annum)
427,000	0.3	+ £ 3.2 m[1]	7,686	+ £ 1.8 m	4,270
	0.5	- £16.6 m[2]		- £ 9.2 m	
	0.7	- £36.4 m		- £20.2 m	

[1] +£ = Increased cost compared to current test

[2] -£ = Saving compared to current test

Figure 1a: New MRSA test used for diagnosis (compared to current test)

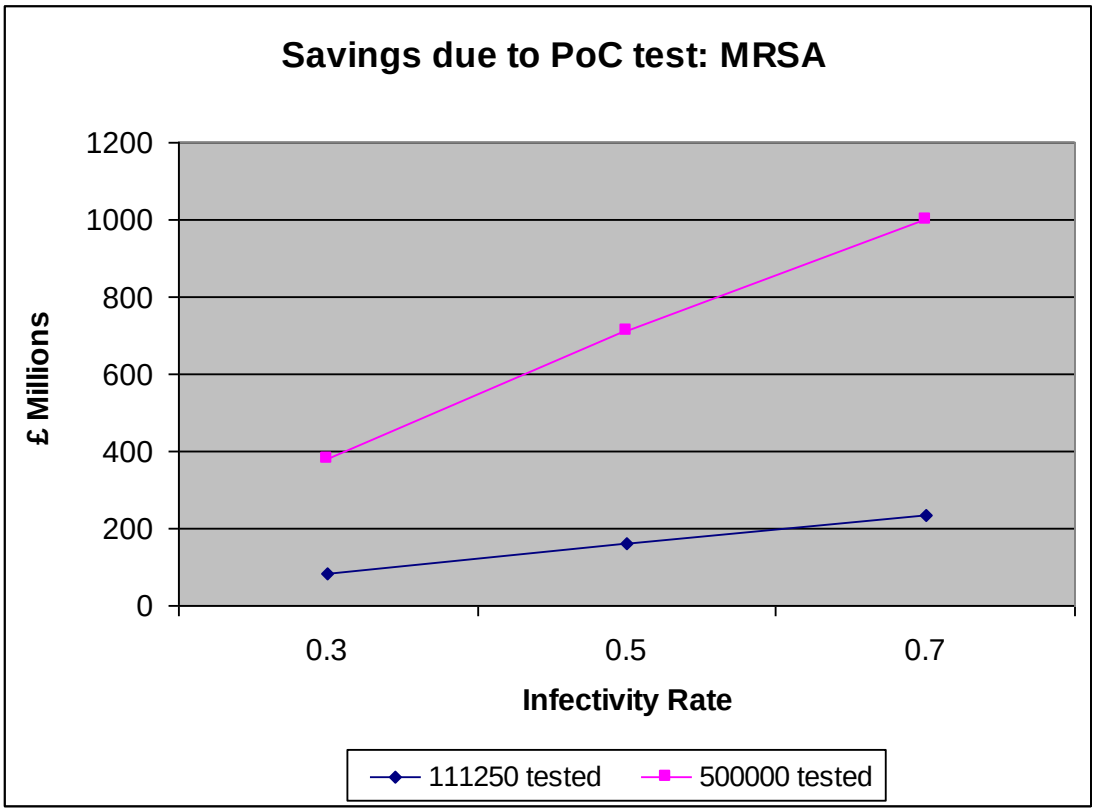
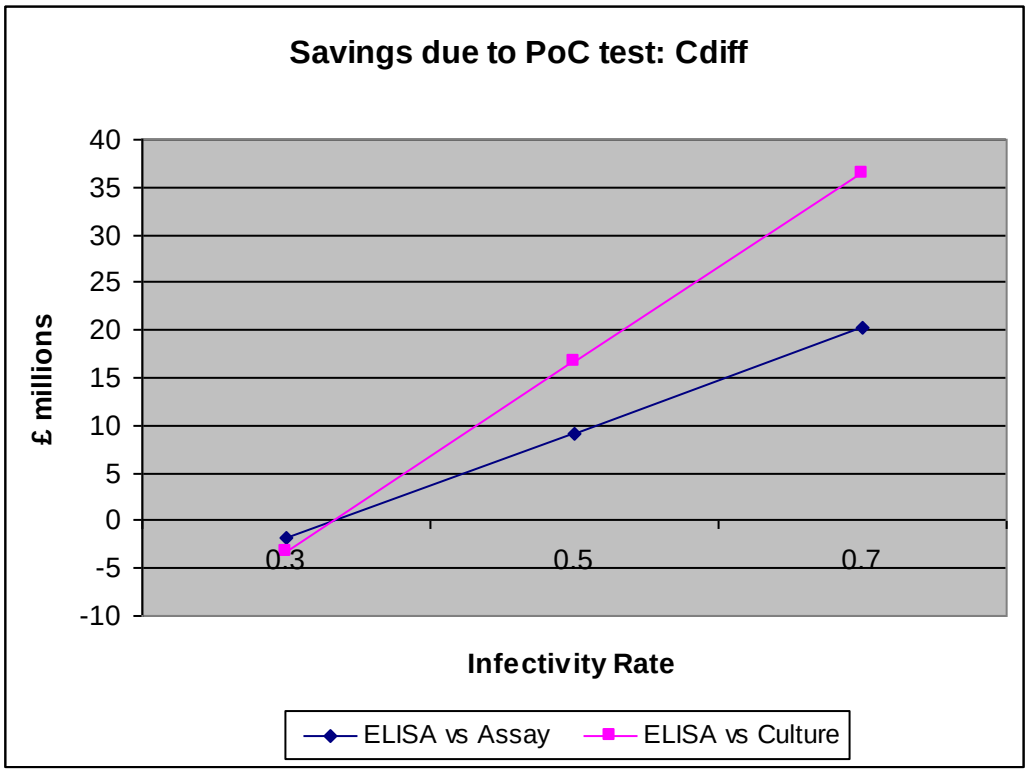


Figure 1b: New *C. difficile* test used for diagnosis (compared to current test)



Annex 1a: MRSA Treatment and Diagnosis Cost Estimates: Input parameters and assumptions

TREATMENT	Source	Unit cost/number	Total annual cost (UK)	Comment
Inpatient episodes			**£106.75 million**	
		22,250 MRSA infections per year in England @ £4,798 per case.		
Decolonisation treatment			**£6.9 million**	
		£7.60 per patient. 11 million elective patients screened. 7% true positive rate. Allowing for false +ves = 907,100@£7.60		
TOTAL TREATMENT		**Inpatient costs + decolonisation**	**£113.65 million**	

DIAGNOSIS	Source	Unit cost/number	Total annual cost (UK)	Comment
Agar			**£623,890**	
		£7.80 (positive), £5.06 (negative) 1 sample per patient, 20% positive: Average cost: (0.2×£7.80)+(0.8×£5.06) 111,250 patients tested (based on 22,250 MRSA infections)	£5.61 per patient £623,890	
Broth enrichment			**£846,390**	
		£10.16 (positive), £6.97 (negative) 1 sample per patient, 20% positive: Average cost: (0.2×£10.16)+(0.8×£6.97) 111,250 patients tested (based on 22,250 MRSA infections)	£7.61 per patient £846,390	
TOTAL DIAGNOSIS			**£623,890 - £846,390**	

CURRENT SCREENING				
Screening tests			**£68.34 million**	
		Elective agar: 10.5 million patients Positive: 735,000@£7.80 Negative: 9,765,000@£5.06 Elective PCR: 0.5 million patients Positive: 35,000@£26.4 Negative: 465,000@£26.4	 £5.73million £49.41 million £0.92 million £12.28 million	

GRAND TOTAL (CURRENT)		**Inpatient costs + decolonisation + diagnostic testing + screening electives**	**£69 million**	

FUTURE SCREENING*				
All screening tests (by 2011)			**£181.88 million**	
		Rapid PCR: £26.46 per test 4.7 million emergency patients@£26.46 11 million elective patients: Positive: 770,000@£7.80 Negative: 10,230,000@£5.06	 £124.08 million £6 million £51.8 million	
Extra decolonisations			**£2.50 million**	
		7% of 4.7 million emergency patients 329,000@£7.60		
TOTAL ADDITIONAL SCREENING (2011)			**£126.58 million**	
		4.7 million extra screened @ £26.46 329,000 extra decolonised @ £7.60	£124.08 million £2.50 million	

***** Excludes diagnostic test costs

Annex 1b: *C. difficile* Treatment and Diagnosis Cost Estimates: Input parameters and assumptions

TREATMENT	Source	Unit cost/number	Total annual cost (UK)	Comment
Inpatient care			**£202.0 million**	
		Additional cost: £4,300 per CDI case Assume 80% cases lead to no re-admission 80%*42,700 hospital acquired cases	£146.9 million	
Re-admissions (extra)			**£55.1 million**	
		Assume 20% CDI cases lead to re-admission Average cost per CDI case raised to: £6,450 Total inpatient: 20%*42,700@£6,450	£55.1 million	

DIAGNOSIS	Source	Unit cost/number	Total annual cost (UK)	Comment
Current testing			**£4.3 million**	
		427,000 @ £10	£4.3 million	

GRAND TOTAL		Inpatient costs + readmissions + diagnostic tests	£206.3 million	

Annex 1c: ESBL Treatment and Diagnosis Cost Estimates: Input parameters and assumptions

TREATMENT	Source	Unit cost/number	Total annual cost (UK)	Comment
Inpatient care			**~£247 million**	
		Additional cost: £8,225 per ESBL case Assume 30,000 cases	~£246.75 million	

DIAGNOSIS	Source	Unit cost/number	Total annual cost (UK)	Comment
Current testing			**N/A**	
		N/A	N/A	

GRAND TOTAL		Inpatient costs + screening/diagnostic tests	> £247 million	

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