Extended spectrum B-lactamase (ESBL) producing E.coli

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Hosted by Lauren Tew
British Teleclass Organizing Committee

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What are Beta-lactamases ?

- Enzymes produced by bacteria
- Break down the B-lactam ring
- Eg in Penicillin
- Some have an "extended spectrum" and break down more agents eg cephalosporins

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ESBL Evolution

- Mid 1980s
- Variants of TEM and SHV
- Breakdown 3rd generation cephalosporins
- Mainly in hospital Klebsiella
- Spread world wide

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Spread of CTX-M

- Cefotaximases
- CTX-Modifying (CTX-M)
- Late 1990s – Many parts of the world
- 2000-1 – First UK isolates (Klebsiella)
- 2003 onwards – widespread across UK
- Especially CTX-M-15

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CTX-M evolution

- 40 enzymes since 1986 largely in last 3 years
- 5 subgroups:
  - CTX-M1(inc.15- India,Poland, Bulgaria,France, Japan) Far East
  - CTX-M9Korea
  - CTX-M8(Kluyvera georgiana homology)
  - CTX-M25 Birmingham, UK
  - CTX-M2(K.ascorbata) S America. Far East

Bonnet AAC Jan 2004

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The British national CTX-M15 E.coli outbreak January 2003- September 2004

- Strain A O25, with IS26, usually gentamicin S:
  - 12 labs 33% referrals:
  - >300 cases in 3 centres >250miles apart
- Strains B O25, no IS26, often gentamicin R:
  - >50 labs 33% referrals, (occasional CTX-M3)
- Diverse strains;
  - >50 labs. 95% usually CTX-M1, rarely CTX-M 9group.
  - Updated from: Woodford N et al. 2004.J Antimicrob Chemother **54**:735-743

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Why are ESBL- producers a problem?

- Confer resistance to cephalosporins, penicillins & penicillinase inhibitors
- Often have multiple resistance
- Spread to commonest species : E.coli
- Asymptomatic pre- & post- infection carriage
- Recognition/testing problems
  - Some apparently susceptible to 1st/2nd gen cephalosporins

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ESBL producing E coli in Shropshire England

- Emerging problem since 2003
- Hospital and community infections
- Several control measures introduced
- Describe our local experience

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Maps of Europe and Shropshire, UK.

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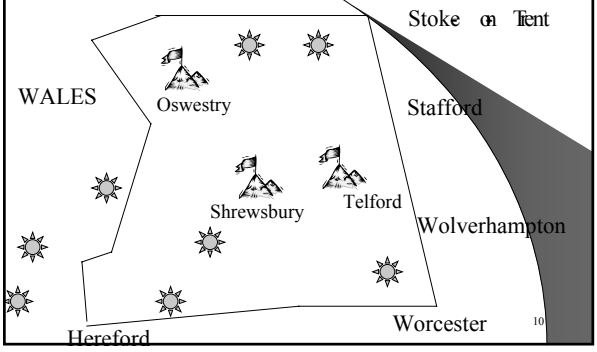
Shropshire geography:



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Shropshire hospital setting

- 540,000 population.
- 2 general hospitals 300 & 520 beds 18 miles apart
  - –7 intermediate care hospitals : 3 in Wales
  - – specialist 230 bed spinal injury & orthopaedic hospital.
  - –12% single rooms
  - –Minimal neutropenia / transplantation.

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Start of the Shropshire 2003 outbreak

- Multi-resistant UTIs in community patients emerging problem early May 2003 – computer search shows emergence from Jan 2003
- Two E.coli strains both resistant to quinolones, cephalexin and trimethoprim, one gentamicin resistant.
- Both sensitive to nitrofurantoin & carbapenems
- Cefpodoxime resistant but clavulanate enhanced (ESBL)

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Quinolone resistant cefpodoxime resistant but non-ESBL producing E coli

- Not O25
- Cefoxitin resistant (unlike ESBL)
- Half trimethoprim susceptible
- 26 PFGE typed.
  - 18 unique
  - 4 pairs
  - No epidemiological association between pairs
- Same therapeutic implications
- Co-selected?

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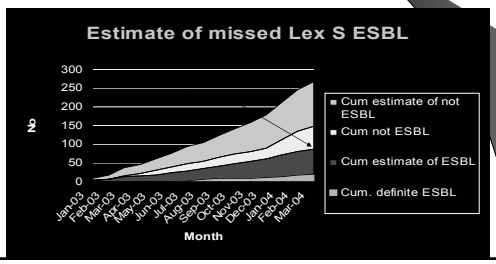
Quinolone R Cephalexin S Urinary E coli

- Jan 2003 to Mar 2004
- 562 isolates, 370 patients
- 27/98 patients with TriR NitS strains ESBL



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Insertion sequence (Is26) issues

- In Shropshire O25 cluster
- In Group A inserted between ISEcp1 and beta-lactamase-CTX-M-15
- Associated with 8- fold decreased MIC to ceftazidime, cefotaxime, cefpodoxime & cefalexin.
- Marked change in antibiotic disc zone sizes sufficient to cause error

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Shropshire case definition

- ESBL cases defined as:

  New cases of infection with E. coli

  With ESBL and resistance to quinolones (and trimethoprim in urine)

  Diagnosed in the Shropshire laboratory since January 2002.

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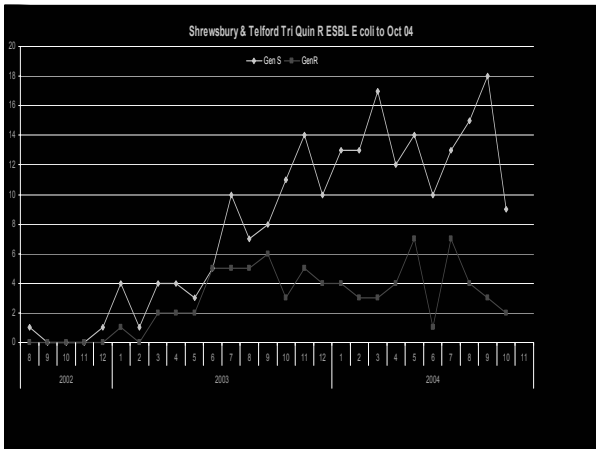

Shropshire outbreak of ESBL producing E coli.

- 364 clinical cases (infections) 1 Jan 03 to 30 Sep 04
  - 68% female, mean age 74 years
  - 49% community samples/51% acute trust samples
  - 85% community previously hospitalised.

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E.S.B.L producing E coli in Shropshire

- Mainly causes urinary tract infections but have also post-operative wound infections, pneumonia and septicaemia.
- Malignancy, diabetes, dementia

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Early Findings

- Gentamicin sensitive strain initially apparent as a community problem.
  - samples from GPs and few from psychiatric hospital.
  - Only 1 nursing home resident.
  - No apparent serious cases.
- Gentamicin resistant strain mainly in Telford Hospital.

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The evolution of the outbreak – Clinical and epidemiology 1.

- In-patient cases initially in Telford area.
- Later spread across the county
- No obvious ward focus (21wards)
- 90% Hospital contact in past 3 years
- But in 10% cases no local acute hospital contact.

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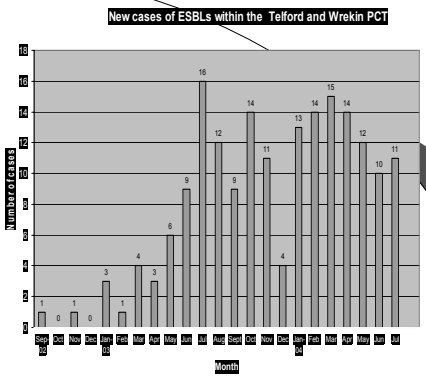

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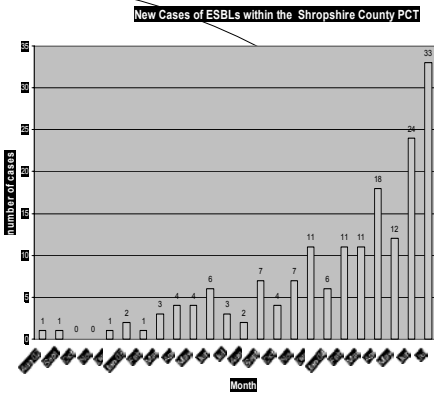

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E.S.B.L producing E coli in Shropshire

- Where did it come from ?
- Not alone – Southampton + Belfast have identical strain to our gentamicin sensitive isolates ("strain A")
- 70 labs across UK
- ? Food source

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Response to the outbreak .1

- Community/Hospital outbreak team (Aug 03)
- Letter to consultants/GPs Sept 03
- Restrictive antibiotic reporting
- Increased use of carbapenems
- Cases isolated in side rooms

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Less obvious serious infections

- First 105 cases, mainly UTI – 28 deaths
- Only 5 had bacteraemia- 2 died
- Case note review by GH and REW
- 16/21 causal/associated with death
- Reported as a "Serious Untoward Incident" to StHA
- External review by Prof Gary French

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Response to the outbreak .2

- March 2004 new hospital antibiotic guidelines introduced and strongly promoted

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Antibiotic Policy changes

- Nitrofurantoin substituted for quinolones in UTIs
- Imipenem substituted for quinolones in routine reporting serious sepsis
- Ertapenem introduced
- Gentamicin substituted for cephalosporins in surgical prophylaxis/serious sepsis
- Return to amoxycillin in respiratory tract infections

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Response to the outbreak .3

- Increased use of hand gel
  - Hand gel by each bedside
- Marking of patient's electronic records
- Daily computer search for re-admissions
- "ESBL management unit"
  - Cohort ward
  - Opened May to June 04
  - Re opened October 04

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Further review of deaths

- 87 deaths out of the 326 cases to August 04
- Case note review and data collection of 50 deaths
- Major burden
  - One third discharged then died: GP records
  - 10 death certificates mention UTI + 2 septicaemia
- External review by Prof French
  - Direct mortality of 19%

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"Community" cases of ESBL producing E.coli – associated features

- Follow-up of 73 (62%) cases April-June 2004
  - 19% in residential/ nursing home
  - 59% had underlying medical conditions
  - 38%, only, of patients had classical UTI symptoms
  - 82% had been treated with antibiotics
  - Initial antibiotics used norfloxacin, trimethoprim and cephalexin

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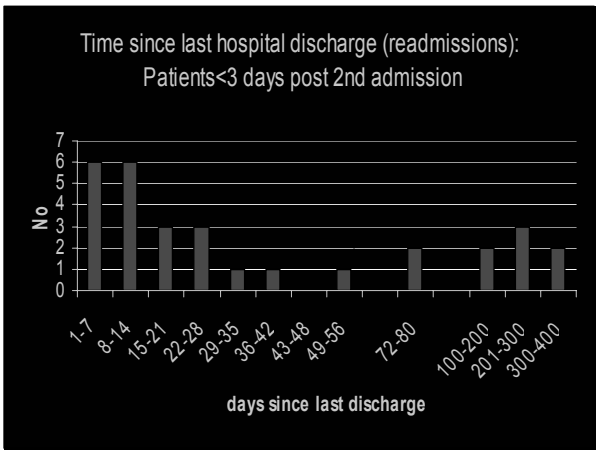
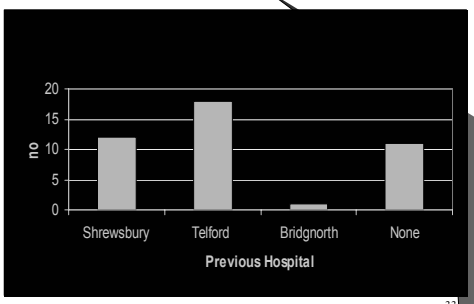


Community acquired ??

Patients tested within 3 days of admission



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The iceberg of faecal colonisation

Opportunistic tests:	No.tested	Positive	% Positive
3 Local Hospitals	291	15	5.2%
3 Local communities 7/11 not hosp assoc.*	475	11	2.3%

- * 4 unrelated types (1 Thailand, 1 RAF),
- 1 E coli O25 Group B (Nepal)
- 2 E coli O25 Group A (1 recent typhoid non UK)
- So IMPORTATION of non-clonal types?

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Bacteraemias

- 24 patients, 27 bacteraemias throughout period
- 19 the isolates was the patient's first isolate
  - Often associated with urinary infection
- 12 bacteraemic patients dead
  - (0,1,1,2,12,14,24,28,43,58,159,217 days post)
- 10 patients had gentamicin resistant strains
  - 5 deaths/10 vs 7/14 gentamicin susceptible strains
  - (0,2,14,43,159 days post)

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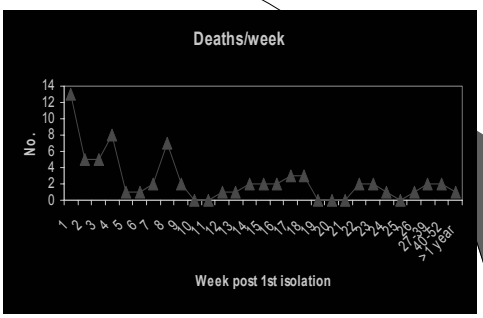
Mortality after initial isolation: Non bacteraemias.



?Relevance to attribution/underlying disease

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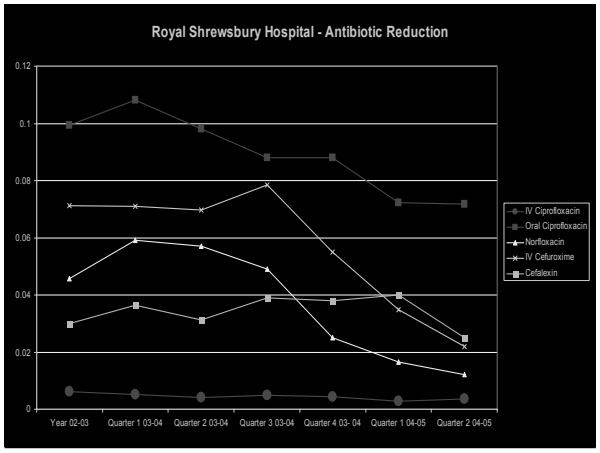
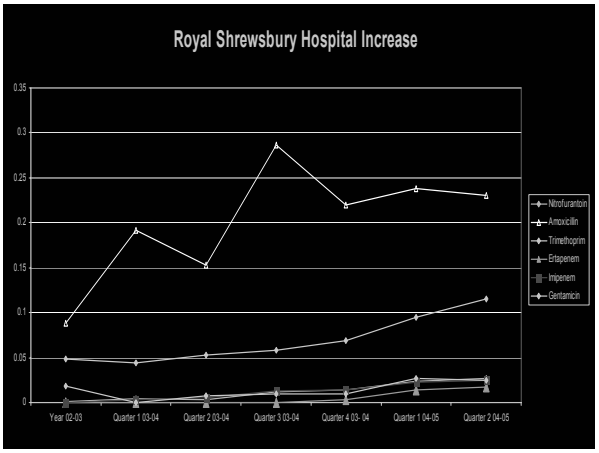
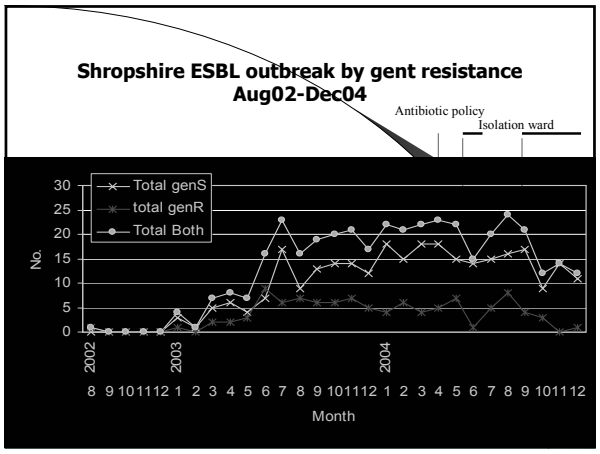
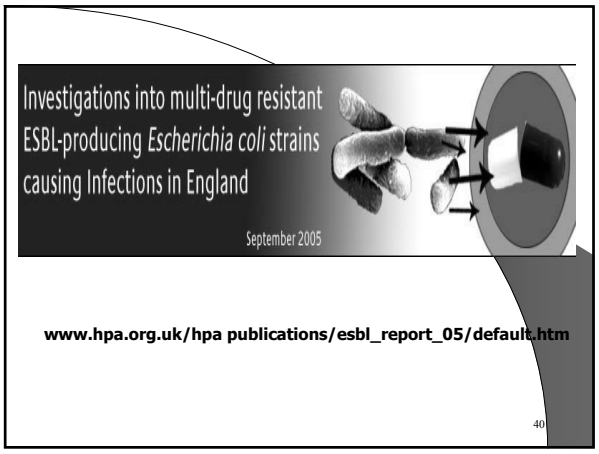
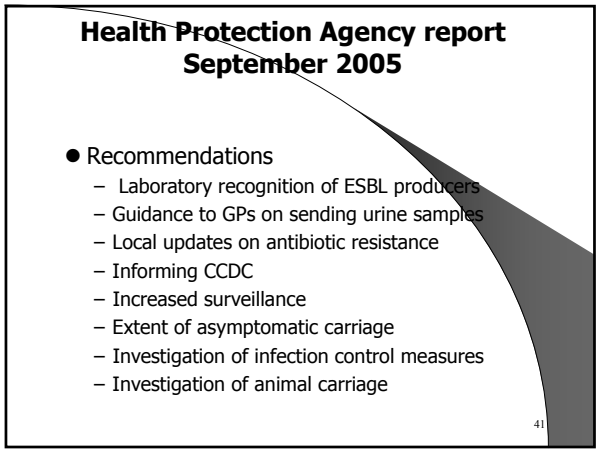

Royal Shrewsbury Hospital - Antibiotic Reduction
0.12
0.1
0.08
0.06
0.04
0.02
0
Year 02-03
Quarter 1 03-04
Quarter 2 03-04
Quarter 3 03-04
Quarter 4 03- 04
Quarter 1 04-05
Quarter 2 04-05
IV Ciprofloxacin
Oral Ciprofloxacin
Norfloxacin
IV Cefuroxime
Cefalexin


Royal Shrewsbury Hospital Increase
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Year 02-03
Quarter 1 03-04
Quarter 2 03-04
Quarter 3 03-04
Quarter 4 03- 04
Quarter 1 04-05
Quarter 2 04-05
Nitrofurantoin
Amoxicillin
Trimethoprim
Ertapenem
Imipenem
Gentamicin


Shropshire ESBL outbreak by gent resistance
Aug02-Dec04
Antibiotic policy
Isolation ward
Total genS
total genR
Total Both
No.
30
25
20
15
10
5
0
2002
2003
2004
8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12
Month


Investigations into multi-drug resistant ESBL-producing Escherichia coli strains causing Infections in England
September 2005
www.hpa.org.uk/hpa publications/esbl_report_05/default.htm
40


Health Protection Agency report
September 2005
Recommendations
– Laboratory recognition of ESBL producers
– Guidance to GPs on sending urine samples
– Local updates on antibiotic resistance
– Informing CCDC
– Increased surveillance
– Extent of asymptomatic carriage
– Investigation of infection control measures
– Investigation of animal carriage
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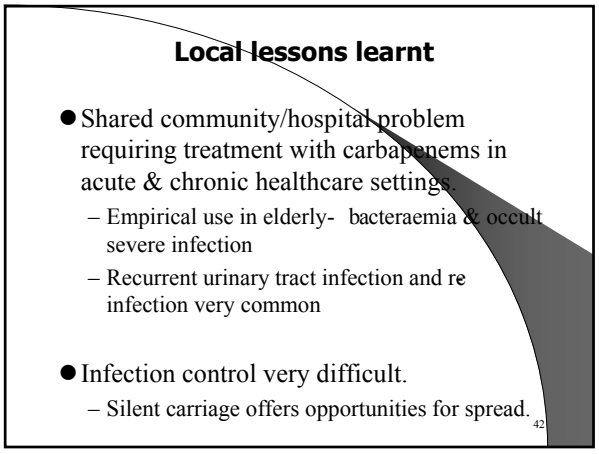
Local lessons learnt
Shared community/hospital problem requiring treatment with carbapenems in acute & chronic healthcare settings.
– Empirical use in elderly- bacteraemia & occult severe infection
– Recurrent urinary tract infection and re infection very common
Infection control very difficult.
– Silent carriage offers opportunities for spread.
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Conclusion

- Ertapenem and Imipenem are likely to replace cephalosporins for empirical therapy in the face of a rise in CTX-M ESBLs & AmpC in E coli.
  - Trimethoprim /quinolone resistance of ESBLs limits therapeutic options
  - Role of older agents such as aminoglycosides needs review –can they be used to spare carbapenems?
  - Need for oral carbapenems/ & study of cephalosporin + B lactamase inhibitors

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Acknowledgements

- Dr Rod Warren, Director of Pathology, Shrewsbury & Telford Hospital.
- Dr Rob Carr HPA CCDC Shropshire,Chair Community Outbreak control team.
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- Dr David Livermore and Dr Neil Woodford. Antibiotic Surveillance and Reference Laboratory, CPHL,Colindale.

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