Institution: University of East Anglia		
Unit of Assessment: 1 - Clinical Medicine		
Title of case study: Improving Clinical Outcomes for Patients with Hard-to-Treat Antimicrobial Resistant Infections		
Period when the underpinning research was undertaken: 2013 to 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Prof David Livermore	Professor of Medical Microbiology	Sept 2011 to Present
Period when the claimed impact occurred: August 2013 to October 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Antibiotic resistant (AMR) pathogens are responsible for millions of hard-to-treat, hospital-acquired infections - 1.7 million in the US and 2.6 million in Europe - that are often fatal. Severe or high-risk multi-drug resistant infections are currently treated by carbapenem antibiotics as drugs of last resort, but resistance to these drugs is escalating rapidly. The impact of Livermore's research is: (i) contributing to the development of novel alternative antibiotic candidates to replace antibiotics of last resort such as carbapenems, including two that are now approved and in clinical use (2020) on a global stage; (ii) the design of bespoke individual antibiotic regimes which have informed practitioners and both enhanced and saved the lives of patients with life threatening infections; (iii) the implementation of a toolkit to reduce carbapenem resistant infections in UK hospitals by improving infection control procedures and policies in the health care sector across the UK.

2. Underpinning research

Antimicrobial resistance (AMR) is a major threat to global health, reducing treatment options and recovery, and with annual death rates in excess of 99,000 (USA) and 37,000 (Europe). Until the turn of the 21st century, carbapenem antibiotics were a '**last resort'** drug used to treat AMR Gram-negative pathogens that cause serious, hard to treat infections. However, as global levels of AMR infections increased significantly there has been a transition to the use of carbapenems as **first-line** treatment options. This has led to the emergence of dangerous carbapenem resistant pathogens, which are extremely difficult to treat. **Livermore's** research has mapped the global emergence of resistance mediated by plasmids encoding carbapenemase genes. **Livermore** discovered how microbes that employ carbapenemase enzyme to break down carbapenem antibiotics are spreading these carbapenemase resistance genes on a global stage, including the Indian Subcontinent, Europe and the UK. The spread of carbapenem resistance poses a significant challenge to vulnerable hospitalised patients and to the first-line antibiotic treatments being used (**3.1**). Understanding the mechanism and dynamics of AMR spread is a critical first step in the design and delivery of prospective new antibiotic therapies, enabling pharmaceutical companies to decide which new candidate should be prioritised in clinical trials. In December 2019, there were 41 new antibiotic candidates in this Global Antibiotic Drug Discovery Pipeline, including some novel combination drug therapies with carbapenems. **Livermore** has performed *in vitro* antibiotic resistance analysis on nine novel antibiotic candidates or novel drug combinations currently either under development or under license by six different, international, pharmaceutical companies. These candidates represent new treatment options after all other treatment options have failed: drugs of last resort. These international pharmaceutical companies include, Merck & Co. Inc, Shionogi & Co. Ltd, & Wockhardt Ltd that are discussed in detail in Section 4 (**3.2, 3.3, 3.4, 3.5**).

Between 2011-18 **Livermore**, was seconded to Public Health England (PHE), for 1.5 days per week (2013-2018 >GBP186,000 to UEA) to chair the weekly surveillance meetings for bacterial pathogens sent in by English hospitals. In 2013 this role led, to a key epidemiological surveillance review that assessed global levels of AMR including carbapenem resistance in Gram-negative pathogens (**3.1**). The conclusion of the research was that there were limited treatment options and a paucity of new drugs in the Antibiotic Drug Discovery Pipeline. Therefore, infection control had to become a primary mechanism for combatting AMR. In 2014 **Livermore** was part of an expert

group that developed a set of recommendations and a toolkit for English hospitals to combat AMR by improving infection control and reducing levels of antimicrobial prescribing in a secondary care setting to preserve the efficacy of Carbapenems to treat infections (**3.6**).

Livermore's significant contributions to the study of AMR both nationally and internationally is evidenced by the British Society for Antimicrobial Chemotherapy (BSAC) Garrod Medal in 2018, the highest honour afforded by the Society. Livermore was listed among Clarivate Analytics most Highly Cited Researcher in 2017, 2018 and 2019.

3. References to the research

3.1 Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, Cornaglia G, Garau J, Gniadkowski M, Hayden MK, Kumarasamy K, **Livermore DM,** Maya JJ, Nordmann P, Patel JB, Paterson DL, Pitout J, Villegas MV, Wang H, Woodford N, Quinn JP. *The Lancet Infectious Diseases*, **2013,**13(9),785–796. DOI: 10.1016/S1473-3099(13)70190-7

3.2 Activity of MK-7655 combined with imipenem against Enterobacteriaceae and Pseudomonas aeruginosa.
Livermore DM, Warner M, Mushtaq S.
Journal of Antimicrobial Chemotherapy, **2013,** 68(10), 2286-2290. DOI:10.1093/jac/dkt178.

3.3 In Vitro Activity of Cefiderocol, a Siderophore Cephalosporin, against Multidrug-Resistant Gram-Negative Bacteria.
Mushtaq S, Sadouki Z, Vickers A, **Livermore DM**, Woodford N.,
Antimicrobial Agents and Chemotherapy, **2020**, 64(12) e01582-20.
DOI: 10.1128/AAC.01582-20.

3.4 In vitro activity of cefepime/zidebactam (WCK 5222) against gram-negative bacteria.
Livermore, D. M.; Mushtaq, S.; Warner, M.; Vickers, A.; Woodford, N.
Journal of Antimicrobial Chemotherapy, **2017**, 72(5), 1373–1385. DOI: 10.1093/jac/dkw593.

3.5 Potential of high-dose cefepime/tazobactam against multiresistant Gram-negative pathogens. J Antimicrob Chemother.
Livermore DM, Mushtaq S, Warner M, Turner SJ, Woodford N.
Journal of Antimicrobial Chemotherapy, **2018**, Jan 1;73(1):126 -133.
DOI: 10.1093/jac/dkx360.

3.6 Prevention and control of multi-drug-resistant Gram-negative bacteria: recommendations from a Joint Working Party
Wilson, A.P.R., **Livermore, D. M.**, et al.
Journal of Hospital Infection, **2015**, 92 Supplement 1, S1-S44.
DOI: 10.1016/j.jhin.2015.08.007.

4. Details of the impact

Livermore's research has led to both the generation of new antibiotics and treatment options, as well as the adoption of measures to prevent the spread of AMR infections in secondary care settings. This has been of benefit to pharmaceutical companies, medical practitioners treating patients with life threatening infections, hospital management who manage the treatment of patients with life threatening infections in secondary care settings, as well as the patients with antibiotic resistance infections.

Discovering New Antibiotics and Treatment Options

Impact on Industry Practice

Two drug candidates, for which **Livermore** performed and published *in vitro* analysis (**3.2, 3.3**) have recently been approved for clinical use (Fetroja (Cefiderocol - Shionogi ltd) and Recarbio (MK7655 with imipenem - Merck & Co. Inc)). These two drugs represent a significant breakthrough for previously untreatable urinary tract and hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia caused by highly resistant gram-negative pathogens. Both drugs are considered as drugs of last resort (**5.1**, **5.2**). Fetroja (Shionogi ltd) is the first new treatment which provides coverage against all Gram-negative pathogens considered of critical priority by

the World Health Organization. It was given FDA approval in the US in 2019 (> USD10,000 treatment course) and European Union Approval for use in 2020 (**5.2**). Recarbrio (Merck & Co. Inc) (> USD7,000 treatment course) has been designed for use in patients aged 18 and above with limited or no alternative therapies (**5.2**). The Committee for Medicinal Products for Human Use – part of the European Medicine Agency- that grants approval to new drugs stated that for the drugs Recarbrio and Fetroja (**5.2**)*:*

> *"Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of […] is favourable in the following indication; Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options*." European Agency Assessment report for Recarbrio (pg. 277) and Fetroja (pg. 155) (**5.2**).

Two other candidates analysed by **Livermore** are in Phase 2 trials including WCK4282 (**3.5**) (a high dose combination of cefepime-tazobactam) and WCK6777 (ertapenem-zidebactam) produced by Wockhardt. Emphasising **Livermore's** role, The Chief Scientific Officer of Wockhardt states:

> "*Dr Livermore's work has provided independent, valuable scientific evidence for substantiating the unmet need addressed by Wockhardt's three antibiotics [WCK4282* (**3.2**)**,** *WCK6777, WCK5222* (**3.4**)*] that target Gram-negative pathogens*" and "*we recognise that Prof Livermore is a world-renowned expert in this area and our collaborations have been extremely fruitful and together we have made great progress in our hunt for new antibiotic drugs to tackle the unmet need of antimicrobial resistance and the growing need for new drugs*" (**5.3**).

Wockhardt's investment in AMR is the largest program anywhere in the world. 'Wockhardt's' CEO commented on their drug portfolio which contains the three drugs analysed by Livermore:

> "*In 2019-20 our sales were $440 m* [USD440,000,000] *(Rs 3325 Crore). It is a matter of great pride that we are now the only company in the world to hold QIDP (Qualified infectious disease product) status for six antibiotics, three of which target Gram Negative pathogens while the other three target Gram Positive difficult-to-treat 'Superbugs'*" (**5.3**).

Global Phase 3 studies for WCK4282 and WCK6777 have been held back by the COVID pandemic but hope to be re-established in 2021. WCK6777 has received the Qualified Infectious Disease Product ('QIDP') from the United States Food and Drug Administration indicating. The QIDP status provides fast track approval to drugs that are effective against a set of multi-drug resistant pathogens, which have a high degree of unmet need in the treatment of infected patients. (**5.3**) The Chief Scientific Officer of Wockhardt (**5.3**) states that:

"*Livermore's studies of one of these drugs WCK4282 reaffirmed the clinically interesting aspects of this antibiotic as a work horse antibiotic used against hard-to-treat Gram negative pathogens*"

He also describes the potential benefit of the third Wockhardt drug WCK5222 (cefepime-zidebactam) (**3.4**) as "*WC 5222 meets the urgent threat of Carbapenem-Resistant Enterobacteriaceae and serious threats like multidrug-resistant Acinetobacter and multidrug-resistant Pseudomonas aeruginosa. It is positioned as a novel MOA-based, high-efficacy destination therapy for XDR pathogens beyond the treatment scope of existing products in the US and Europe. The investigational product is manufactured for Phase III trials at FDA-approved contract manufacturing sites in Europe. An abridged Phase III global study protocol has been finalised in consultation with US FDA, European Medicine Agency (EMA) and Chinese regulator, National Medical Products Administration (NMPA)"* (**5.3**).

Impact on Patient care: Saving lives of Patients with Hard-to-Treat Life Threatening Infections

Livermore's expertise in identifying and interpreting resistance mechanisms of pathogenic bacteria was invaluable in guiding treatment of specific patients, some with life-threatening infections (**3.1**). During **Livermore's** part-time secondment to PHE (1.5 days per week from 2011-18) he was frequently (often on a weekly basis) consulted by clinicians to use his expertise and knowledge to advise on unconventional regimens for infection caused by multidrug-resistant pathogens, where standard treatment options had been exhausted. It sometimes included compassionate use of developmental agents prior to licensing. Three such examples (**5.4a-c**),

have been published as patient case notes where bespoke antibiotic drug regime led to successful patient outcomes. The Director for the Centre for Clinical Infections and Diagnostics Research, a consultant microbiologist at Guy's & St Thomas' Hospital states that "*one such case study was a 78-year-old woman who was admitted to the intensive care unit at London Bridge Hospital with aortic valve endocarditis that was not controlled by all currently available antibiotics and therefore life-saving surgery to replace the heart valve could not proceed. Blood cultures grew an extremely drug-resistant (XDR) Pseudomonas aeruginosa due [..]that we rarely see in the UK. The patients was colonised with other resistance bacteria that complicated the situation (Klebsiella pneumoniae with OXA-48 carbapenemase and Acinetobacter baumannii with OXA-23/OXA-51 A). Discussion led to a decision to make a successful, formal request for compassionate use of cefiderocol (subsequently licensed under the trade name Fetroja) after* ***David [Livermore]*** *had arranged urgent susceptibility testing of cefiderocol to confirm its activity against the isolate. Two days after starting cefiderocol treatment the septicaemia was stopped and aortic valve replacement could proceed with a successful outcome. It is highly likely that without this successful treatment plan this patient would not have survived. This was a particularly successful case which illustrates the path we have to follow, that* ***David [Livermore]*** *has helped with over the years at multiple stages*" (**5.4a**).

Implementing a New Tool; Acute trust toolkit for early detection, management and control of carbapenemase-producing Enterobacterales; Impact on infection prevention and management

Livermore's research highlighted the scale, mechanism and global spread, of rapidly emerging multi-drug resistant carbapenemase-producing organisms (**3.1**). **Livermore's** research expertise in this area and his secondment role with PHE informed 1) the updated screening criteria for suspected cases of carbapenem resistant infections including travel from abroad including Indian subcontinent 2) guidance on the therapies to be prescribed to treat carbapenem resistant infections, 3) advice on monitoring infection trends in trusts and robust diagnostic plans using laboratory services. In 2013, **Livermore** was invited to join a British Working Group commissioned by PHE. This group outlined AMR concerns and developed a **toolkit** (published 2014) (**5.5** designed to prevent and reduce the spread of carbapenemase-producing Enterobacterales (CPE) infections in health and residential care settings. This was a key pathway to raising awareness of CPE infection and prevention methods in Trusts across England as evidenced by widespread uptake of the toolkit into local trust guidelines (**5.5**). The Director for the Centre for Clinical Infections and Diagnostics Research, a consultant microbiologist at Guy's & St Thomas' Hospital states "*the toolkit they published in 2014 to reduce the spread of carbapenemase-producing Enterobacteriaceae […]is a landmark reference document on which the framework for infection control of CPEs is based at probably all NHS hospitals including our own"* (**5.4**). The toolkit advised front line staff about the 1) early detection of these infections through early recognition of individuals who may be colonised 2) improved laboratory screening methods for these infections 3) prevention and control of infections through enhanced cleaning and decontamination protocols 4) isolation procedures for patients with infections. It also provided a series of checklists for the Trust Boards, Executive and IP&C teams to ensure effective infection prevention practices are in place within Trusts and information sheets on CPE infections for patients and families. An accompanying letter to the toolkit from the Chief Executive of PHE sent to all Trusts in England stated that: "*The toolkit is intended to provide a framework to support local risk assessment, providing the minimum interventions required to safeguard patient safety and prevent an escalation of the problem*" (**5.5**).

A 2019 PHE commissioned quantitative evaluation of the toolkit in all English trusts (**5.8**) showed;

- 92% of Trusts, implemented or wrote new local prevention plans based on this toolkit;
- 75% reported consistent compliance with screening and isolation of CPE risk patients outlined in the toolkit.

A qualitative evaluation was undertaken on the implementation of the toolkits in 2017 based on 44 interviews with staff from 12 Acute Trusts. This report includes a statement that one Trust used the toolkit *'to inform and check their own CPE prevention, management and control plans in particular in the event of an outbreak*' (**5.7** pg. 18). In addition, the toolkit has been used as a catalyst for change and influenced individual trusts to change their funding priorities.

"*The CPE toolkit was seen as a credible source of information, which could help to secure management support for financial investments to address resource challenges such as a shortage of isolation facilities or funding for additional training' (***5.7** pg 6) Individual hospital trusts have also provided accounts of how they have implemented the toolkit. The Royal Wolverhampton Trust UK, reported to its Trustee's that "*So far there have been 12 patients identified as having CPE-producing organisms in the New Cross Microbiology Laboratory [..] So far during 2014 there have been two incidents during which the toolkit has had to be actioned and these account for four of the twelve patients. Local application of the toolkit has been successful in these instances, and there is no evidence of widespread dissemination of these resistant organisms*' (**5.9**).

In October 2020, this toolkit was updated and published as a new document '*Framework of actions to contain carbapenemase-producing Enterobacterales* that also draws on **Livermore's** research (**3.6**). This update was in response to the published evaluation reports (**5.7, 5.8**) and feedback from key stakeholders requesting one document in a simplified format that provides a framework of actions for all health and social care providers in acute and non-acute settings. The objectives of the new framework are the same namely 1) to provide a framework of actions and tools to support health and social care providers 2) support development of local guidance and tools for the early detection of CPE with the aim of preventing transmission and containing their spread for the safety of patients and the wider population 3) direct health and care professionals to the relevant guidelines for laboratory methods, including reporting of results to PHE. The original Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae has also been used to develop similar, specific toolkits for Scotland in 2017, Wales in 2018 and for non-acute and community settings in England 2019 (**5.6**). Finally, in 2020 the Department of Health and Social Care changed its policy on notifiable diseases stating '*Acquired carbapenemase-producing Gram-negative bacteria to the list of causative agents which, when identified in a human sample, **must be notified** by the operator of a diagnostic laboratory to Public Health England (PHE)'* (**5.10**).

5. Sources to corroborate the impact

5.1 PEW Charitable Trust report (Dec 2019) and articles on Tracking the Global Pipeline of Antibiotics in Development.

5.2 European Agency Assessment and U.S. Food and Drug Administration approvals for Recarbrio and Fetroja (2019-2020).

5.3 Testimonial letter from the CEO of Wockhardt (10.12.2020).

5.4 Case report for bespoke treatment option (Cefiderocol), 2019 and testimonial letter from the consultant (24.02.2021).

5.5 PHE Chief Executive Letter (27.02.2014) to accompany the Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae (2013) from page 4.

5.6 Toolkits for the early detection, management and control of carbapenemase producing Enterobacteriaceae in Welsh and Scottish (from page 45) acute settings and non-acute and community settings in England (from page 92).

5.7 Schneider et al: Implementing a toolkit for the prevention, management and control of carbapenemase-producing Enterobacteriaceae in English acute hospitals trusts: a qualitative evaluation (BMC Health Services Research, 2019).

5.8 Coope et al: An evaluation of a toolkit for the early detection, management, and control of carbapenemase-producing Enterobacteriaceae: a cross-sectional survey of NHS acute trusts in England (Journal of Hospital Infection, 2018).

5.9 The Royal Wolverhampton Trust UK, report to its Trustees on the implementation of the toolkit (June 2014).

5.10 Department of Health and Social Care announcement of new Notifiable Disease (2020).