Institution: King's College London		
Unit of Assessment: 1		
Title of case study: Transforming the global diagnosis of Sepsis, its immunological characterisation and clinical management		
Period when the underpinning research was undertaken: 2016 – 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:**
Manu Shankar-Hari	NIHR Clinician Scientist; Professor of Critical Care Medicine	2009 – to date
Adrian Hayday	Professor of Immunobiology	1998 – to date
Period when the claimed impact occurred: 2016 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Sepsis is one of the most common but least treatable causes of death in hospitals worldwide. Part of this situation stemmed from the lack of an agreed international definition of sepsis and septic shock, which would allow robust diagnosis and patient management. King's has led on the redefinition of sepsis, initiated the UK's first epidemiological study on long-term outcomes, and characterised the associated immune response. This work led to a new internationally adopted clinical definition (within the ICD-11 classification), championed by the WHO to recognise sepsis as a global health priority. It has informed healthcare policies and clinical management of sepsis patients and survivors globally. Most recently, King's expertise has been applied to support the UK's clinical response to COVID-19.

2. Underpinning research

Sepsis is a severe response of the human immune system to bacterial and viral infections. We commonly consider bacterial infection when thinking about sepsis, but severe COVID-19 is a typical example of viral sepsis. In the 2017 Global Burden of Diseases report, there were nearly **50 million cases of sepsis and 11 million resultant deaths worldwide** (85% of which occured in low- or middle-income countries). The fundamental challenge to clinicians is how to diagnose and treat this condition. This impact case focuses on work addressing three related clinical problems, based on the premise that robustly defining ('benchmarking') the diagnosis of sepsis and its clinical management is a highly effective way to improve patient survival. This was previously lacking because: (i) there was no universally accepted clinical definition of sepsis; (ii) there were no agreed clinical diagnostic measures of sepsis; (iii) there were no drugs of proven value to treat the immune response to sepsis. **Consequently, this made sepsis one of the most common but least treatable causes of death in hospitals.**

Before 2016 diagnosis of sepsis was inconsistent globally. There was no international agreement on clinical diagnosis of sepsis based on patient examination, as symptoms differ between patients, leaving diagnosis up to individual clinician's judgement. Without a definition, it was impossible to standardise the World Health Organisation (WHO) International Classification of Disease (ICD) coding of sepsis in hospitals to allow international benchmarking, comparison of global incidence and treatment, and, ultimately, improve patient outcomes. Consequently, there was also no national data from England on what happens to sepsis survivors once discharged from hospital, and how the longer-term prognosis for sepsis survivors compares to other high-income countries. King's researchers and others internationally recognised the need to re-define sepsis and septic shock (referred to as Sepsis-3 definitions hereon).

In 2016, King's work re-defined sepsis as 'life-threatening organ dysfunction due to the body's response to infection'. Kings researcher Shankar-Hari led the redefinition of Septic Shock as part of a 16-member international expert panel (Task Force) – convened by the European Society of Intensive Care Medicine and the (US) Society of Critical Care Medicine –

and for the first time, generated explicit clinical criteria for septic shock diagnosis **(1, 2)**. Shankar-Hari went on to help write the Task Force Sepsis Definitions document, for use by clinicians globally. This work used an innovative mix of scientific methods to systematically analyse global epidemiological and clinical records to arrive at the new definition and clinical criteria. A combination of analysis of systematic reviews, a Delphi process to generate expert consensus, and data analyses of nearly 4.5 million sepsis incidents worldwide – none of which had previously been applied to septic shock – gave powerful and robust results **(1, 2)**.

Kings researchers used this new definition to analyse patterns in sepsis survival in England. They **led the first UK epidemiological study** to examine the long-term outcome for sepsis survivors. Using data from the ICNARC database on nearly 700,000 critical care admissions (between 2009 and 2014) in England, King's identified 94,748 sepsis survivors. They showed that amongst this group, when followed up over a 5-year period, 15% of sepsis survivors die in the first year following hospital discharge, with 6-8% dying yearly over the next 5 years. Furthermore, nearly a third of these sepsis survivors are hospitalised again within 90-days of being discharged **(3)**. These results led the researchers to design and clinically validate a sepsis survivor score, which estimates prognosis for the first year based on follow-up care **(4)**.

Identifying diagnostic biomarkers for early detection of the immune response associated with sepsis. While there are known differences between the signatures of the immune response to sepsis and to non-infectious severe conditions such as major trauma, there was previously no consensus on which measurable indicators of clinical illness (referred to as biomarkers) are useful as diagnostic tests for sepsis. King's researchers recognised the need for biomarkers that reliably differentiate which patients with infection will go on to develop sepsis, and also to identify which of these biomarkers are specific for sepsis to differentiate it from other inflammatory conditions. To do this first required a standardised assessment of the immune system across many patients and so in 2018, King's led the first UK study to profile immune cells in this cohort, using flow-cytometry. King's identified three potential biomarkers that could predict which of those patients requiring emergency care and with an infection, would go on to develop sepsis **(5)**. Importantly, it also laid foundations for large scale immunological profiling for the assessment of sepsis and, more recently, COVID-19 at King's.

Synthesising evidence for clinical practice on the use of corticosteroids to treat the immune response to sepsis. There were no drugs proven to favourably change the severe immune responses in sepsis to benefit patients. Corticosteroids are cheap, globally available, and early evidence suggested they were a potential treatment; however, the largest RCTs had given mixed outcomes, so there was an urgent need to assess all evidence systematically in order to make clinical recommendations. Based on his expertise in clinical sepsis research, Shankar-Hari was recruited to an international expert panel; having commissioned a systematic review of latest evidence, the panel co-authored a BMJ rapid recommendation clinical practice guideline on corticosteroid therapy for adult sepsis patients. It recommended that corticosteroid therapy in sepsis may reduce duration of septic shock **(6)**.

Responding rapidly to assess the immune response of COVID-19. When the pandemic arrived in the UK, King's researchers worked closely with emergency care and infection diseases clinicians at Guy's & St Thomas' NHS Foundation Trust (GSTT) to assess the immune system changes associated with COVID-19 infection using their earlier sepsis studies as the foundation (COVID-IP, a collaboration between King's, GSTT and The Francis Crick Institute led by Prof Hayday). This provided the largest (at that time) comprehensive assessment of immune biomarkers of severe COVID-19 (based on 63 adult patients admitted to GSTT), identifying those biomarkers associated with poor prognosis, those that are similar to sepsis, and those that help predict the immune response **(7).** Kings were also the first to report immunological changes observed in the rare COVID-related illness, Multisystem Inflammatory Syndrome in Children (MIS-C), revealing it was a serious immunopathological condition distinct from Kawasaki's disease despite superficial resemblance **(8).**

3. References to the research

1. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775-87.

2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
3. Shankar-Hari M, Harrison DA, Ferrando-Vivas P, Rubenfeld GD, Rowan K. Risk Factors at Index Hospitalization Associated With Longer-term Mortality in Adult Sepsis Survivors. JAMA Netw Open 2019;2:e194900. doi.org/10.1001/jamanetworkopen.2019.4900
4. Shankar-Hari, M., Rubenfeld, G.D., Ferrando-Vivas, P., et al. Development, Validation, and Clinical Utility Assessment of a Prognostic Score for 1-Year Unplanned Rehospitalization or Death of Adult Sepsis Survivors. *JAMA Netw Open* 3, e2013580 (2020).
5. Shankar-Hari M, Datta D, Wilson J, et al. Early PREdiction of sepsis using leukocyte surface biomarkers: the ExPRES-sepsis cohort study. Intensive Care Med 2018; 44(11): 1836-48;
6. Lamontagne F, Rochwerg B, Lytvyn L, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ (2018)
7. Laing, A.G.*, et al.* A dynamic COVID-19 immune signature includes associations with poor prognosis. *Nat. Med.* **26**, 1623-1635 (2020).
8. Carter, M.J.*, et al.* Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat. Med.* 26, 1701-1707 (2020).

4. Details of the impact

Following the publication of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016 **(1, 2)**, the major elements of international classification, policy and clinical guidance for sepsis which affect clinical care worldwide, have been changed. This has impacted national and international levels of healthcare policy and clinical management of sepsis.

Impact on international health policy and clinical management of sepsis

The revised sepsis definitions were adopted as the new International Classification of Diseases standard (ICD-11) [A]. The ICD coding system is used for classifying all diseases globally, overseen by the WHO, who describe the ICD as '*the foundation for the identification of health trends and statistics globally, and the international standard for reporting diseases and health conditions. It is the diagnostic classification standard for all clinical and research purposes*.' In May 2019, the WHO's World Health Assembly officially adopted ICD-11, directly drawn from King's research **(1,2)**. The ICD is used to underpin comparisons of health data (local, regional, national, international), in analysis that informs evidence-based decision making and policy development, and to monitor the incidence, prevalence and causes of disease. The ICD is also used to determine the Global Burden of Disease estimates of sepsis (a tool widely used by policymakers). WHO regulations ensure Member States use the most current ICD revision to record and report mortality and morbidity statistics, nationally and internationally: since the previous 1990 endorsed version, the system has been used by more than 150 countries and translated in over 40 languages.

The new definitions both support and help deliver on the WHO commitment to make sepsis a global health priority [B]. In 2017, the WHO highlighted the updated sepsis definitions as the diagnostic gold standard and recognised sepsis as a global health priority - a year after publication of pivotal research led by King's researchers. Later that year the WHO Assembly adopted resolution WHA70.7 on 'Improving the prevention, diagnosis and clinical management of sepsis'; this urged member states to '*apply and improve the use of the International Classification of Diseases system to establish the prevalence and profile of sepsis*' **[B.2]**. In 2020, the progress report on this resolution specifically notes that the '*WHO published the International Classification of Diseases, 11th Revision, allowing reporting of sepsis, in conjunction with the underlying infection'*, as a milestone towards estimating the global burden of sepsis more accurately **[B.3]**. The WHO factsheet on sepsis also explicitly references King's research **(1, 2) [B.1]**.

The new definitions underpin the WHO's first global epidemiological report on sepsis. In September 2020, the WHO published its first 'Global report on the epidemiology and burden of sepsis'. When the report was launched the WHO Director-General said: *"The world must urgently step up efforts to improve data about sepsis so all countries can detect and treat this terrible condition in time"* **[C.1]**. This report enabled for the first time the gathering of global epidemiological data in sepsis incidence and outcome – and it noted that data was still incomplete and patchy, highlighting the need for more action. To address this, the WHO proposed using the ICD-11 going forwards to standardise diagnosis, treatment and reporting across regions in order to *'Improve*

surveillance systems, starting at the primary care level, including the use of standardized and feasible definitions in accordance with the International Classification of Diseases (ICD-11), and leveraging existing programmes and disease networks' **[C.2]**.

Impact of new ICD-11 definition for healthcare systems and professionals. The establishment of the ICD-11 definition of sepsis benefits national organisations that influence health policy to improve patient care. These definitions were endorsed by the UK's Academy of Medical Royal Colleges and 30 equivalent national or regional societies from all WHO health regions (including the USA, Europe, Japan, China, Caribbean, Pan Arabic Critical Care Society, India) **[D.1]**. Following these endorsements, these Professional bodies and patient advocacy groups (for example the UK Sepsis Trust) have used the new sepsis definitions to lobby governments for improved management of sepsis patients **[D.2].** These definitions are now used for diagnosing and treating sepsis patients in all these countries such that they have contributed to the quantitation of worldwide sepsis incidence and outcome statistics in the widely used WHO Global Burden of Disease **[D.3]**. The new definitions were also adopted by the International Surviving Sepsis Campaign (SSC) guidelines in 2016 **[D.4].** The SSC is a global initiative of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) at 200 sites internationally, to measure and compare changes in adherence to sepsis quality of care indicators, aiming to reduce mortality and morbidity from sepsis.

Impact on Sepsis patient management in the UK

The Intensive Care National Audit and Research Centre database ICNARC is the national audit for all 235 UK NHS Trusts (98% coverage of adult general critical care units in England, Wales and Northern Ireland), that assesses the outcome and care quality of adult critical care units in the UK every year. Shankar-Hari is a Senior Clinical Scientist at ICNARC and led the study that is currently used to benchmark sepsis between different intensive care units in England, Wales and Northern Ireland **[E.1]**. This King's-led work described how to operationalise the international benchmarking of sepsis incidence and outcomes **[E.2]**. Since 2019, these methods are used for the national patient-centred safety and quality of care policy, funded by the UK Government (Getting It Right First Time) which expects hospitals to adapt their sepsis management procedures in line with the CQUIN report (NHS Commissioning for Quality and Innovation) **[E.3, E.7].** This exemplifies a change of the implementation of national level benchmarking of critical care units to improve clinical care of sepsis patients (data on the effect of implementing this change in the UK is not yet available and will be highly skewed by COVID-19). In 2019, Shankar-Hari also collaborated with NHS Digital to extract all known sepsis events in the UK (2011-2017), in order to generate a measure of sepsis disease burden in the UK used to inform health policy **[E.4-E.6]**.

Impact of King's-led research on patient care and outcomes of sepsis

King's expertise leads to the development of patient-centred clinical resources. The BMJ rapid practice recommendations provide guidance for clinicians on how best to treat patients with corticosteroids, based on critical appraisal of all available evidence **(6)**. This coproduced research involved sepsis survivors and caregivers as well as healthcare professionals, and explicitly developed recommendations taking into account patient outcomes and patient preferences – for example, giving options which make a distinction between reducing the chance of death and quality of life. The resulting guidelines on corticosteroid therapy for sepsis patients are intended for use by clinicians, explicitly involving patients and carers in the decision-making process. BMJ guidelines – patient and practice-changing focused – are widely adopted, influencing patient care internationally **[F.1]**. Based on the findings on sepsis survivor care and prognosis **(4)**, King's developed a prognostic tool. This clinically-validated sepsis survivor score provides estimates of prognosis for the first year post-sepsis based on follow-up care, and can be used by clinicians/patients to anticipate risk and manage the follow-up care of sepsis survivors based on risk, for the first time. This open-access score has been endorsed by the UK Intensive Care Society for use by UK clinicians **[F.2]**.

Raising awareness amongst clinicians, sepsis survivors and the public of health risks. In the UK, few patients who survive sepsis-related critical illness are given follow-up care, and King's research highlighted that one in six sepsis survivors die in the first subsequent year **(3,4)**. To increase public awareness and lobbying to address this at a national level, King's have engaged extensively with the media on this important patient centred issue, with this specific study being

covered by 86 National and International Newspapers and numerous blogs in 2019 **[G.1].** Furthermore, focus groups of clinicians, sepsis survivors and their families revealed much greater awareness of the risk of future morbidity and mortality, and the need for close monitoring **[G.2]**.

Using sepsis expertise to inform the clinical response to COVID-19. King's research on the immunophenotyping of Sepsis and COVID-19 **(5,7,8)** has had several early impacts in 2020, with Professor Shankar-Hari taking leadership roles in the national response due to his expertise in the field of sepsis. Given his role in identifying long-term risk factors in sepsis survivors, his expertise was sought as part of the WHO international Long COVID Committee, which was tasked with the clinical characterisation of Long COVID and the ICD11 coding also directly informed WHO COVID information (2020) **[H.1]**. As a result of the COVID-IP and MIS-C studies, Professors Shankar-Hari and Hayday were invited to give evidence to the House of Lords Science & Technology Select Committee on the immunology of COVID-19 in June 2020 **[H.2]**. Furthermore, King's work led to strategic investment of USD20 million by NIH to understand the pathology of MIS-C and pilot treatments **[H.3]**.

5. Sources to corroborate the impact

[A] Details of the International Classification of Diseases (ICD-11) [PDF]

[B] Evidence of World Health Organisation policy changes on sepsis: **B.1** WHO Sepsis Factsheet; **B.2** WHO Assembly resolution WHA70.7 'Improving the prevention, diagnosis and clinical management of sepsis') May 2017 (p3, point 8); **B.3** Progress Report 2020 [PDF]

[C] Evidence on global epidemiology of sepsis: **C.1** WHO Press release 'WHO calls for global action on sepsis - cause of 1 in 5 deaths worldwide' (2020); **C.2** WHO Global Report on the Epidemiology and Burden of Sepsis (2020) (reference 3, p. 14, 42) [PDF]

[D] Evidence of impact of new ICD-11 definition for healthcare systems and professionals: **D.1** National and international Society endorsements associated with reference (1); **D.2** NHS Blog Post on sepsis by the Medical Director for Clinical Effectiveness at NHS England; **D.3** Details on the Global Burden of Disease; **D.4** International Surviving Sepsis Campaign (SSC) guidelines: Rhodes A, et al. Intensive Care Med (2017), 43(3): 304-77 [PDF]

[E] Evidence of impact on sepsis patient management: **E.1** Shankar-Hari, M et al., (2017) Br J Anaesth. 1;119(4):626-636; **E.2** Ranzani et al., (2019) Crit Care Med. 47(1):76-84; **E.3** Details of the national Getting It Right First Time programme; **E.4** NHS Digital collaboration on UK sepsis disease burden**; E.5** Secretary of State for Health & Social Care tweet on introduction of new sepsis guidance (2019); **E.6** Guardian Article on NHS sepsis guidance (2019); **E.7** NHS Commissioning for Quality and Innovation (CQUIN) reports (2016-2020) [PDF]

[F] Evidence of impact on patient-centred resources: **F.1** Details on the patient and practice focuse BMJ rapid reccomendations; **F.2** The sepsis prognosis tool website and ICS endorsement [PDF]

[G] Increasing patient and public awareness: **G.1** Examples of press coverage on calls for better sepsis survivor follow up care; **G.2** Sepsis survivors and clinicians focus group reports [PDF]

[H] Evidence of impact during COVID-19 response: **H.1** King's contribution to WHO Long-Covid committee (WHO Report: Expanding our understanding of post COVID-19 condition – Annex 2; **H.2** Overview and transcript of expert evidence to House of Lords Science & Technology Select Committee 'Science of COVID-19 inquiry', 15th June 2020; **H.3** NIH Director's blog announcing investment of £20m treatment-focussed funding [PDF]