Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Reducing the burden of viral hepatitis globally

Period when the underpinning research was undertaken: January 2014 - June 2019

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:
Graham Cooke	Professor of Infectious Diseases	2006 - present
Timothy Hallett	Professor of Global Health	2004 - present
Maud Lemoine	Professor in Hepatology	2011 - present
Shevanthi Nayagam	Clinical Fellow	2017 - present
Mark Thursz	Professor of Hepatology, Head of Department	1991 - present

Period when the claimed impact occurred: 2015 – 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Viral hepatitis is a major and growing contributor to global mortality (~1.5 million deaths in 2013). Research at Imperial generated estimates of its global burden and devised strategies to reduce incidence of new cases and deaths. These underpin the WHO hepatitis B and C strategy, targets and monitoring framework for elimination; were used by Gavi to support the global introduction of hepatitis B birth-dose vaccination; supported the inclusion of tenofovir-based treatment in China's national insurance programs leading to a reduction in cost to patients from CNY49.0 to CNY16.6 per day; and supported a WHO recommendation for general population screening of hepatitis B in low-income settings.

2. Underpinning research (indicative maximum 500 words)

In 2014 the World Health Assembly urged progress on combatting viral hepatitis. In response, Imperial researchers sought to understand the global burden of hepatitis (1), finding that mortality from viral hepatitis ranked seventh amongst all diseases globally. They also found that over the preceding twenty-five years the number of deaths due to viral hepatitis had increased in contrast with the reductions in deaths attributed to other major infectious diseases. The key determinant of this trend was the lack of scale-up of effective treatments, and population growth and ageing in countries with high burdens of Hepatitis C.

To understand how this challenge could be responded to, information about the global epidemics of Hepatitis B (2) and C (3) and possible interventions were synthesised to create model-based projections for the impact of a package of interventions. This revealed five priority areas: (i) three-dose hepatitis B vaccine for infants, (ii) the timely birth dose for the prevention of mother-to-child transmission of hepatitis B, (iii) blood and injection safety, (iv) harm reduction services for persons who inject drugs, and (v) diagnosis and treatment. The analyses indicated that with service coverage in each program area exceeding particular levels, substantial reductions in the incidence of new cases (90% on 2010 levels) and deaths (65% on 2010 levels) could be achieved by 2030. The team also estimated a 'global price tag' for this strategy and showed how these costs were dependent on drug prices and the cost of

screening strategies for those at risk. In further work the impact of Gavi contributing to the funding of the birth dose scale-up in selected countries was estimated.

The researchers worked with authorities in China to assess the cost and impact of incorporating the policy changes into the national program. This implied affording much greater access to tenofovir-based treatment for those living with Chronic Hepatitis B. It was found that adopting the full package of interventions in China would incur a large upfront cost and that if cost for treatment were to fall on patients themselves it may be unaffordable (4). If instead those costs were absorbed in the health sector it was shown that within a decade, they would have been more than offset by the reduced costs associated with treating patients with end-stage liver disease (4). It was concluded that from a societal perspective, there was a favourable long-term 'return-on-investment' of adopting the proposed strategy for combating hepatitis, and that expanding treatment would require the cost of drugs to be covered by the national insurance program (4).

The Imperial-led research showed that screening for infection was key to achieving the targets in the case of both Hepatitis B and C (2, 3). The PROLIFICA trial was established to test the feasibility of general population screening in West Africa (5) and found to be acceptable and feasible. The researchers examined the cost of implementing the program and likely benefits to patients and established that such an approach was also likely to be 'cost-effective' in many low-income settings (6).

3. References to the research (indicative maximum of six references)

(1) Stanaway, J.D., Flaxman A.D., Naghavi, M., Fitzmaurice, C., Vos, T., Abubakar I…Cooke, G.S (2016). The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet*; 10;388(10049): 1081-8. DOI.

(2) Nayagam, S., Thursz, M., Sicuri, E., Conteh, L., Wiktor, S., Low-Beer, D., & Hallett, T.B. (2016). Requirements for global elimination of hepatitis B: a modelling study. *Lancet Infectious Diseases*, 16(12), 1399-1408. DOI.

(3) Heffernan, A., Cooke, G.S., Nayagam, S., Thursz, M., & Hallett, T.B. (2019). Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *Lancet; 393*(10178), 1319-1329. DOI.

(4) Nayagam, A.S., Chan, P., Zhao, K., Sicuri, E., Wang, X., Jia, J., ..., Hallett, T.B. (2020). Investment case for a comprehensive package of interventions against Hepatitis B in China; applied modelling to help national strategy planning. *Clinical Infectious Diseases*; 72(5): 743-752. DOI.

(5) Lemoine, M.N., Shimakawa, Y., Njie, R., Taal, M., Ndow, G., Chemin, I., *et al.*, (2016). Acceptability and feasibility of a screen-and-treat programme for hepatitis B virus infection in The Gambia: the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study. *Lancet Global Health*; 4(8): e559-e567. DOI.

(6) Nayagam, S., Conteh, L., Sicuri, E., Shimakawa, Y., Suso, P., Tamba, S, *et al.* (2016). Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in The Gambia: an economic modelling analysis. *Lancet Global Health*; 4(8), E568-E578. DOI.

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4. Details of the impact (indicative maximum 750 words)

Burden and Global Strategies

Estimates of the burden of viral hepatitis (1) were used by WHO to make the case for their new advocacy strategy [**A**]. Model-based strategies for eliminating hepatitis as a public health threat and the associated programmatic and epidemiological targets were provided to WHO as an unpublished report (reference 2 in document [**A**]) and subsequently published (2, 3 above). The resulting WHO strategy to achieve elimination of hepatitis B and C by 2030 [**A**] directly cites the outputs from this work - specifically the targets and their associated estimated impact. The construction of the five pillars of the strategy ("*Reaching five prevention and treatment service coverage targets would eliminate hepatitis B and C as public health threats",* page 6*)* directly refers to the modelling research. The economic analyses presented as part of the strategy ([**A**], Section F) directly reproduces analyses undertaken by the researchers. The strategy was presented to the WHO Executive Board in 2015 and subsequently adopted by WHO as the Global Health Sector strategy on viral hepatitis 2016-2021 [**B**]. These programmatic areas and targets are the benchmarks by which WHO monitors progress of countries in respect of its aim to combat hepatitis, as confirmed in a WHO-authored article [**C**]. Today 87% of persons living with hepatitis reside in a country with a national plan for hepatitis [**D**] that is based on, or draws reference from, the WHO health sector strategy [**B**] that the Imperial research directly contributed to. The WHO authors of [**C**] confirm that the targets have led to the initiation of action plans in many countries: "*As a result, many countries have initiated work to formulate national action plans, starting with initial assessments*".

Introduction of Birth Dose Vaccination

As one of three independent modelling teams, the Imperial researchers adapted their model developed in academic references (2,3) and worked with GAVI to provide projections of the impact of the timely birth dose to inform their hepatitis B birth dose vaccine investment case [**E**]. In this it was shown that GAVI support for birth dose introduction could avert between 300,000 and 1,200,000 perinatal infection-related deaths between 2021 and 2035 and that this would be highly cost-effective (USD72-USD403 per death averted). The GAVI investment strategy relied on five primary criteria when ranking proposed new vaccine introductions - two of which (health impact and value for money) directly used the impact and cost-effectiveness estimates that the Imperial team provided [**F**]. Birth-dose hepatitis B vaccine was recommended to the Gavi board for introduction from 2021 and adopted at its November 2018 meeting subject to successful replenishment that has now been confirmed.

Introduction of Tenofovir in Chinese National Insurance Program

Imperial modelling of the need to invest in hepatitis B control in China formed one of the case studies in the WHO advocacy strategy [**A**, Box 4 page 10]. This work was expanded to explore the impact and cost-effectiveness of introducing tenofovir into the Chinese national insurance program. A preprint of this work (subsequently published academic reference 4) was shared with the WHO China office and formed part of a WHO (China) policy brief to government [**G**]. This was the major piece of research motivating a policy change [**H**] whereby tenofovir became included within the Chinese national insurance program [**I**] leading to the reduction in cost of tenofovir for patients from ¥ 49.0 to ¥ 16.6 per day, or less [**I**]. In a study of patients at selected hospitals, the proportion of patients being treated with first-line recommended drugs increased from 41.9% (2010) to 92.8% (2019).

Population-wide screening for HBV in West Africa

The Imperial-led PROLIFICA trial is cited as a case study in the WHO advocacy strategy [**A**, Box 5 page 11]. The evidence that this trial generated on the efficacy and cost-effectiveness of population wide screening for HBV in West Africa is cited in the WHO Guidelines for

screening of hepatitis B and C [**J**]. The WHO is required to consider the cost and feasibility of a strategy it may recommend, and the research at Imperial was the only such information available for low-income countries [**J**, pages 40 and 50]. This research is also reproduced as supporting evidence on cost-effectiveness in the Annex [**J**]. As a consequence of the research, these guidelines gave, for the first time, a 'conditional recommendation' that testing should be made available to the general population in low-income settings with high prevalence of hepatitis B.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] The World Health Organization (2016). Combating Hepatitis B and C to Reach Elimination by 2030. (see page 2, reference 1, Figure 2, page 4, page 6, box 4 on page 10, box 5 on page 11, and section F). Archived here.

[**B**] The World Health Organization (2016). Global Health Sector Strategy on Viral Hepatitis 2016-2021: Towards Ending Viral Hepatitis. Archived here.

[**C**] Hutin Y. J-F., Bulterys M., Hirnschall G.O., (2018) *How far are we from viral hepatitis elimination service coverage targets?* *JOURNAL OF THE INTERNATIONAL AIDS SOCIETY*. 21(S2): e25050. DOI.

[**D**] Smith S., Harmanci H., Hutin Y., Hess S., Bulterys M., Raquel Peck et al., (2019). Global progress on the elimination of viral hepatitis as a major public health threat: An analysis of WHO Member State responses 2017. *JHEP Reports* 2019. DOI.

[**E**] GAVI (2018). Hepatitis B Birth Dose Investment Case at the Vaccine Investment Strategy Programme and Policy Committee Meeting. Annex C. Archived here.

[F] GAVI (2018). Vaccine Investment Strategy. Archived here.

[**G**] The World Health Organization China (2015). Policy Brief: The case for investing in hepatitis B and C treatment in China. Archived here.

[**H**] Letter from Dr Bernhard Schwartlander (WHO Representative in China during the work, now Chef Du Cabinet, WHO).

[**I**] Liu J., Liang W., Jing W., Liu M. (2019) Countdown to 2030: eliminating hepatitis B disease, China. *BULL WORLD HEALTH ORGAN* 97:230–238.

[**J**] The World Health Organization. Guidelines on Hepatitis B and C testing. February 2017 (page 40 and 50). Archived here.