Institution: University of Cambridge		
Unit of Assessment: 2 Public Health, Health Services and Primary Care		
Title of case study: Controlling HIV through evidence-based prevention strategies		
Period when the underpinning research was undertaken: 2008-2020		
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:**
Daniela De Angelis	Professor	April 2011-date
Anne Presanis	Senior Statistician	2007-date
Period when the claimed impact occurred: 2013-2019		
Is this case study continued from a case study submitted in 2014? N		

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

University of Cambridge research has played a fundamental role in the control of HIV by developing tools to enable monitoring of infection in the population worldwide, informing the design of disease control strategies, and evaluating what works. Cambridge approaches have been adopted by Public Health England, the European Centre for Disease Control, and other international bodies as their methods of choice. These approaches have contributed to improvements in the quality and quantity of life for thousands of HIV-infected individuals and reduced HIV spread, helping to place the UK on track to eliminate transmission of HIV by 2030.

2. Underpinning research (indicative maximum 500 words)

Strategy to control a global epidemic: early diagnosis and early treatment

There is no cure or vaccine for HIV, a global epidemic that has so far infected 76 million people, killed 33 million people, and cost the global economy hundreds of billions of pounds. A key disease control strategy involves early HIV diagnosis and lifelong use of highly effective anti-viral medicines. This approach demonstrably reduces viral transmission, prevents illness, and prolongs life (*Lancet* 2013). However, its success depends on being able to reliably monitor HIV rates in the population, identify high-risk groups, and design and evaluate strategies to reduce transmission.

Challenges of monitoring HIV in populations

The monitoring of HIV poses significant challenges because the infection often remains undetected due to its long incubation period. This means that it is impossible to directly measure key quantities that are essential to disease control, such as prevalence (the number of people infected), incidence (the number of new infections), and numbers of undiagnosed infections. Relevant information that could be used to indirectly estimate these quantities exists – but it is imperfect. It is typically affected by biases and is scattered across many disparate sources, such as registers from sexual health clinics, surveys and expert beliefs. If the available information is naïvely combined, without attention to the strengths and weaknesses of the different data sources, the results can be misleading.

Research led by the Medical Research Council Biostatistics Unit (MRC-BSU) at the University of Cambridge has addressed these challenges. The Cambridge team has developed new statistical approaches that combine different data sources and account for the uncertainties and limitations that affect each source. The tools that the team has produced inform infection control strategies by enabling the monitoring needed to make them effective, and by generating evidence that these strategies improve quality of life, prevent illness, prolong life, and save money.

Producing robust methods and tools for evidence-based strategic decisions for HIV disease control

Since the early 2000s, Cambridge researchers have developed surveillance tools that enable tracking of HIV in the population. The methods are based on Bayesian statistical models [1,2] that allow judicious combination of multiple different sources of current and prior knowledge through formal statistical “triangulation”. This approach to estimating prevalence and incidence is particularly important in a field like HIV, where a wide range of data sources exists, but each data source has known limitations and biases. Through use of Bayesian methods, the tools

make it possible to formally account for these limitations and to correct for biases by incorporating additional information from other datasets or from expert opinion.

The first tool, the **Multi-Parameter Evidence Synthesis (MPES)** [1,3,4] model, triangulates 11 current datasets, including routinely collected data on the numbers of people living with diagnosed HIV, records from sexual health screening, and information from community surveys, with evidence from previous studies, to estimate HIV prevalence.

The second tool is a **"back-calculation" approach** [2,5–7] which combines data on new diagnoses and information on HIV disease progression to statistically reconstruct the hidden infection process underlying these observed data and to estimate the number of new infections over time [2].

For over a decade, joint work between MRC-BSU and the government's public health agencies has resulted in regular assessments of the state of the HIV epidemic, published yearly in official Public Health England reports and used to inform policies. Cambridge research has been key in evaluating HIV control strategies, for example showing that they are associated with substantial falls in infection rates, number of late diagnoses, and undiagnosed infections [4,7].

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

1. **De Angelis D**, **Presanis AM**, Conti S, Ades AE. Estimation of HIV burden through Bayesian evidence synthesis. *Statistical Science* 2014; 29(1): 9-17*
2. Birrell PJ, Gill ON, Delpech VC, Brown AE, Desai S, Chadborn TR, Rice BD, **De Angelis D**. HIV incidence in men who have sex with men in England and Wales 2001–10: a nationwide population study. *Lancet Infectious Diseases* 2013; 13: 313–318*
3. Jackson C, **Presanis A**, Conti S, **De Angelis D** (2019) Value of Information: Sensitivity Analysis and Research Design in Bayesian Evidence Synthesis, Journal of the American Statistical Association, 114:528, 1436-1449, DOI: 10.1080/01621459.2018.1562932*
4. **Presanis AM,** Gill OM, Chadborn TR, Hill C, Hope V, Logan L, Rice BD, Delpech VC, Ades AE, **De Angelis D**. Insights into the rise in HIV infections, 2001 to 2008: a Bayesian synthesis of prevalence evidence. *AIDS* 2010; 24(18):2849-58*
5. Brizzi F, Birrell PJ, Plummer MT, Gill ON, **De Angelis D**. Extending back-calculation approaches to jointly estimate age and time specific HIV incidence. *Lifetime Data Analysis* 2019; 25: 757-780*
6. van Sighem A, Nakagawa F, **De Angelis D**, […], de Wolf F, Fraser C, Phillips A. Estimating HIV incidence, time to diagnosis, and the undiagnosed HIV epidemic using routine surveillance data. *Epidemiology* 2015; 26:653-660. doi: 10.1097/EDE.0000000000000324*
7. Brizzi F, Birrell PJ, Kirwan P, Ogaz D, Brown A, Delpech VC, Gill ON, **De Angelis D.** (2020) HIV transmission in men who have sex with men in England: on track for elimination by 2030? arXiv:2010.00740v1, The Lancet HIV (preprint)*.

*These publications have been peer-reviewed, providing evidence of research quality.

Competitive funding awarded

De Angelis, D (Programme Leader). MRC Unit Core Support, GBP16 million, 2018-2023.

De Angelis, D (Programme Leader). MRC Unit Core Support, GBP13 million, 2013-2018.

De Angelis, D (PI). "Evaluation of Interventions". National Institute for Health Research (NIHR) Health Protection Research Unit, GBP3.8 million, 2014-2020.

De Angelis, D (PI). "Statistical inference in transmission models based on Bayesian synthesis of evidence from multiple sources" MRC, GBP200,000, 2007-2010.

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

Controlling HIV through evidence-based prevention and control strategies

HIV is among the deadliest and costliest global epidemics of the past half-century. Around 76 million people around the world have been infected, including 33 million people who have died. An estimated 38 million people currently live with HIV globally, including seven million who are unaware they have the infection (UNAIDS statistics). In the UK, about 100,000 people are living with HIV, with high concentrations among men who have sex with men and among black African populations [A]. Between 2000 and 2015, the HIV epidemic was estimated to cost the global

economy over USD550 billion (Lancet 2018).

For more than a decade, researchers in Cambridge and at Public Health England (PHE) (and its predecessor organisations) have worked closely together to develop and deliver evidence-based approaches to support control strategies for HIV [1–5,7]. The approaches – involving intensification of prevention policies over time, informed by the estimates resulting from the Cambridge methods – have been associated with reductions in HIV transmission and in undiagnosed infections and late diagnoses. They have helped cut infection rates, with numbers of undiagnosed infections reduced by thousands in England alone.

Adopted by the UK and other governments, these approaches are essential to the tracking of HIV in populations, the development and implementation of strategies to reduce HIV spread, and the rapid evaluation of those strategies – all activities that are fundamental to disease control. Cambridge research has therefore contributed significantly to the remarkable improvements seen in the quality and quantity of life for thousands of HIV-infected individuals, to reductions in HIV transmission, and to savings in healthcare costs, placing the UK on track to eliminate transmission of HIV by 2030 [A].

Widespread adoption of Cambridge tools and estimates in the UK and internationally

Public Health England [A–C] has adopted the Cambridge techniques as the official methods for estimating HIV prevalence and incidence. Annual estimation of HIV prevalence in the UK has, since 2005, been based on the Cambridge Multi-Parameter Evidence Synthesis (MPES) approach. The Cambridge back-calculation method has provided incidence estimates since 2012. Both these estimates have been used by PHE to underpin its strategy, policy and practice recommendations [C], becoming an *"essential component of PHE annual reports"* and *"the national yardstick to measure progress"* in controlling HIV [B]. Guidelines from the National Institute for Health and Care Excellence (NICE) on increasing HIV testing uptake (2016) [D], and the British HIV Association UK National Guidelines for HIV Testing (2015, 2017 and 2020) [D], also endorse the Cambridge methods. Internationally, several European governments and agencies have adopted the Cambridge approaches, for example those using the recommended modelling tool of the European Centre for Disease Control, an agency of the European Union (including from Austria, Denmark, Finland, Greece, Malta, the Netherlands, Portugal, Bulgaria, Croatia, the Czech Republic, Slovakia, and Slovenia) [6,E].

A further far-reaching international impact has been through **Fast-Track Cities** [F], a global initiative involving hundreds of millions of people and 300 major cities around the world, led by the Joint United Nations Programme on HIV/AIDS (UNAIDS), the International Association of Providers of AIDS Care, and the United Nations Human Settlements Programme (UN-Habitat). Cambridge's research plays a crucial role in this initiative by informing the targets and monitoring progress towards them, particularly in relation to UNAIDS' 90-90-90 targets: that 90% of people living with HIV should know their HIV status; 90% of people with diagnosed HIV infection should receive antiretroviral therapy; and 90% of people receiving therapy should have sustained viral suppression. Analysis based on Cambridge methods has shown that the **UK met the 90-90-90 target in 2016** [G], while London has exceeded the new 95-95-95 target [F].

Providing evidence for HIV prevention strategies

Evidence produced using tools developed by the Cambridge team has been crucial in **establishing the effectiveness of HIV prevention strategies** and providing the basis for policy intervention. Cambridge evidence was, for example, a key part of PHE's written submission to the House of Commons Select Committee on Health and Social Care's Report on Sexual Health in 2019 [H], used to support the approach of increasing HIV testing and early HIV treatment as prevention.

Since 2010, Cambridge estimates of undiagnosed HIV infections have **underpinned multiple high-profile initiatives in the UK to increase testing**. Examples include the Terrence Higgins Trust's "It Starts with Me" campaign [I], the National HIV Prevention Programme for England [I], and the "Halve It" campaign, a coalition of organisations – including NICE, the Department of Health and Social Care, and the Local Government Association – working with the House of Commons All-Party Parliamentary Group on HIV/AIDS to halve the proportion of undiagnosed

infections by 2020 [I].

Guided by information derived through Cambridge's tools, these campaigns play a major role each year in public health initiatives, such as National HIV Testing Week. The success of these initiatives is evidenced by figures derived using Cambridge's methods, which show a **progressive decrease in the number of undiagnosed infections among gay and bisexual men**, which has halved from around 8000 in 2008 to around 4000 in 2018 [A]. Regular application of the back-calculation approach has shown that the **infection rate in gay and bisexual men has fallen steadily** [A] (from around 2800 in 2012 to around 800 in 2018 – a reduction of over two thirds), with a steep fall in incidence in younger men.

There has also been a steady **decline in the numbers of people receiving late diagnoses of HIV** in the UK, decreasing from 1,861 in 2015 to 1,279 in 2019 [J]. Late (CD4 count <350 cells/mm^3) and very late (CD4 count <200 cells/mm^3) diagnosis of HIV is the most powerful predictor of mortality in infected people. The UK's downward trend in late diagnoses [7] is therefore very important for health outcomes among those who are infected.

Using PHE data [K], it is possible to show what would have happened without intensified prevention after 2010. Assuming that the proportion of very late diagnoses remained constant over time at the level observed in 2010 (28%), an expected (counterfactual) number of very late diagnoses can be derived (Table 1). This suggests that **around 1100 very late diagnoses were averted over the period 2014-18.** From these figures, **a cost saving of over GBP4 million per year can also be estimated**. This cost is calculated as the difference between the respective yearly costs of GBP7.1 million and GBP3.1 million of very late and (comparatively) early diagnoses (Table 2). This offers an approximation of the economic impact of the policies fueled by Cambridge research.

	2010	2014	2015	2016	2017	2018	Cumulative difference
Number with CD4 count	5423	5172	4832	4107	3511	3465	
Number with CD4 <200	1533	1203	1012	943	809	825	
Expected very late diagnoses based on 2010 figures		1448	1353	1150	983	970	
Expected minus observed very late diagnoses		245	341	207	174	145	1112

Table 1. People aged 15 years and over diagnosed at very late stage. Data to end of December 2018. Source: [K].

Cost type	CD4≤200	CD4>200	Cost per annum of very late diagnosis for 1112 people (GBP)	Cost per annum of earlier diagnosis for 1112 people (GBP)
Inpatient	1411	207	1,569,032	230,184
Outpatient	840	628	934,080	698,336
Day ward	318	168	353,616	186,816
Other drug costs	3,070	1,293	3,413,840	1,437,816
Tests & procedures	768	461	854,016	512,632
Total annual	6,407	2,758	7,124,584	3,066,896

Table 2. Annual costs for people living with HIV by CD4 strata and potential costs of illness for averted very late diagnoses of people living with HIV since 2014. Costs are taken from Beck et al. (https://doi.org/10.1371/journal.pone.0027830) and are at 2008 prices. No deflation effect or temporal changes in costs are included.

Supporting bold, ambitious policies to eliminate HIV

The body of work from Cambridge and its collaborators, including PHE, has been highly influential in supporting policy-makers in the shift from a traditional containment strategy to a much bolder strategy of eliminating HIV altogether, particularly since the introduction of UNAIDS' 90-90-90 target in 2016. Led by the evidence produced by Cambridge and the ability to monitor infections effectively, **policies set out by the Department of Health and Social Care now focus on eliminating, not just controlling, HIV** [A].

Cambridge work was used by the Department of Health and Social Care in its decision to establish an independent HIV Commission in 2019 [L], whose remit is to find ambitious and achievable ways to end new HIV transmissions and HIV-attributed deaths in England by 2030. In 2019, PHE cited Cambridge research, methods, tools and estimates [L] in its submission to the Commission.

The HIV Commission's report, published in December 2020 [L], set an interim target of reducing transmission by 80% by 2025. The Cambridge back-calculation estimates were used in the report to show the decline in new infections. The importance of monitoring transmission by estimating incidence is highlighted in the report's recommendation that *"everyone serious about ending new transmissions must track our progress against estimated incidence of HIV, not new diagnoses alone*."

The report also made use of Cambridge estimates of undiagnosed prevalence from Public Health England's latest annual report, including the key headline: "*The message from the HIV Commission is 'test, test, test'. To find the estimated 5,900 undiagnosed people living with HIV in England, HIV testing must be normalised throughout the health service. Everyone should know their HIV status*" [L].

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

A. HIV in the United Kingdom: Towards Zero HIV transmissions by 2030. PHE, 2019 pp. 3, 32, 85
B. Testimonial from PHE Feb 2020
C. **(i)** PHE: Prevalence of HIV infection in the UK in 2018: pp. 2, 5; **(ii)** PHE: Towards elimination of HIV transmission, AIDS and HIV-related deaths in the UK (2018): pp. 48, 49
D. **(i)** HIV testing: increasing uptake among people who may have undiagnosed HIV – NICE guidelines (2016); **(ii)** BHIVA/BASHH/BIA Adult HIV Testing Guidelines 2020: pp. 6, 7, 11, 31
E. **(i)** HIV Modelling Tool - European Centre for Disease Prevention and Control; **(ii)** ECDC HIV Modelling Tool Manual, p. 57 **(iii)** ECDC Continuum of HIV care 2018, p. 8
F. **(i)** Global Fast-Track Cities programme: http://www.fast-trackcities.org; **(ii)** Duncombe C, Ravishankar S, Zuniga JM. Fast-Track Cities, *Current Opinion in HIV and AIDS* 2019;14:503-508. doi: 10.1097/COH.0000000000000583
G. HIV diagnoses continue to fall as UK exceeds UNAIDS target - GOV.UK, Nov 2018: p. 2
H. **(i)** House of Commons Health and Social Care Committee – Sexual Health Fourteenth Report of Session 2017–19: p. 57; **(ii)** Evidence from Public Health England: pp. 3, 6
I. **(i)** It Starts with Me campaign: https://www.startswithme.org.uk/; **(ii)** National HIV Testing Week Round Up (HIV Prevention England, 2017); **(iii)** Public Health England, GBP600,000 funding of 12 projects by PHE to help prevent HIV (2017); **(iv)** Halve It position paper. A roadmap for eliminating late diagnosis of HIV in England (2017)
J. Public Health England. Trends in HIV testing, new diagnoses and people receiving HIV-related care in the United Kingdom (2020)
K. **(i)** https://www.gov.uk/government/statistics/hiv-annual-data-tables; **(ii)** Data provided by Public Health England on number and proportion of adults (aged 15 years and above) diagnosed very late, Dec 2020
L. **(i)** PHE organisational submission to the HIV Commission: p. 7; **(ii)** HIV Commission. How England will end new cases of HIV: Final report and recommendations (2020).pp. 4, 14–15