

<b>Institution:</b> University of Edinburgh		
<b>Unit of Assessment:</b> 1		
<b>Title of case study:</b> C: Accurate estimates of pneumonia disease burden guide child immunisation policy, practice and global investment to reduce child pneumonia mortality		
<b>Period when the underpinning research was undertaken:</b> 2004 – 2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Harish Nair	Chair of Paediatric Infectious Diseases and Global Health	2010 – present
Harry Campbell	Chair of Genetic Epidemiology and Public Health	1995 – present
Igor Rudan	Chair of International Health and Molecular Medicine	2001 – present
Evropi Theodoratou	Chair of Cancer Epidemiology and Global Health	2007 – present
<b>Period when the claimed impact occurred:</b> August 2013 – December 2020		
<b>Is this case study continued from a case study submitted in 2014?</b> Y – <a href="#">REF2014/1/Q</a>		
<b>1. Summary of the impact</b>		
<p><b>Underpinning Research:</b> University of Edinburgh (UoE) researchers provided estimates of global child pneumonia incidence and mortality, including the first global estimates of burden of disease from respiratory syncytial virus (RSV) and influenza. They also provided global and national estimates of burden of disease from pneumococcus, and estimates of the effectiveness of the pneumococcal conjugate vaccine (PCV).</p> <p><b>Significance and Reach of Impact:</b> The estimates informed international priority-setting to scale up PCV coverage. Together, these policy and stakeholder commitments led to 60 additional low-and-middle-income countries adopting PCV between 2013 and 2020, expanding the global PCV coverage from 19% in 2013 to 48% in 2020. By 2018, a total of 183,000,000 children had been vaccinated against pneumococcus. As a direct result of this expansion, across 170 countries globally, there were 1,000,000 fewer child pneumonia deaths between 2013 and 2020 than would have occurred had 2013 mortality rates applied.</p> <p>More than 50 countries have used UoE's approach to measuring influenza disease burden to inform policy, and in 2019, Bhutan began a new influenza child vaccination programme that has reached 90% national coverage.</p> <p>The World Health Organization recognised the RSV vaccine as the highest priority future vaccine in 2015, and in 2018, the Global Alliance for Vaccines and Immunisation prepared a Vaccine Investment Case directly informed by UoE global estimates to support the future introduction of RSV vaccine. The Bill and Melinda Gates Foundation has committed more than USD116,000,000 (GBP84,866,760; 01-21) to large new investments in RSV since August 2013. This coordinated activity of major agencies has resulted in over 40 RSV vaccine candidates being in development in 2018, from none in 2013.</p>		
<b>2. Underpinning research</b>		
<p><b>The Challenge: In 2013 pneumonia was still the largest single cause of child death globally</b></p> <p>Global child pneumonia mortality in 2013 was 1,200,000 per year; down from 2,100,000 in 2000, but still unacceptably high. More than 90% of these deaths occur in children living in low-and-middle-income countries (LMICs). <i>Streptococcus pneumoniae</i> (pneumococcus), <i>Haemophilus influenzae type b</i> (Hib), RSV and influenza are 4 of the major causes. Coordinated action at national and global levels was required to reduce these rates of child pneumonia mortality.</p>		

Given the financial and technical difficulties of gathering national health service data and performing surveillance studies in LMICs, epidemiological models provide essential complementary information for national policy-making, priority setting and programme planning both by the national Ministries of Health in LMICs and by international agencies such as the World Health Organization (WHO), United Nations Children's Fund (UNICEF), World Bank, the Global Alliance for Vaccines and Immunisation (Gavi) and the Bill and Melinda Gates Foundation (BMGF). These models produce regional, global and national estimates of the absolute and relative importance of pneumonia as a cause of death, and of the role of individual pathogens that cause it.

As the leading pneumonia expert group in the WHO Child Health Epidemiology Reference Group (CHERG), UoE researchers Campbell, Rudan, Nair and Theodoratou have conducted 15 years (2005–2020) of international epidemiological research, modelling the burden of disease from child pneumonia, producing more than 20 publications including [including 3.1, 3.3, 3.4 and 3.5]; estimating the effectiveness of PCV immunisation [3.3]; and studying risk factors and burden estimates at national, regional and global levels.

**REF2014: Epidemiological models quantify the high global, regional and national disease burden and estimate vaccine effectiveness to influence international health policy**

In the REF2014 impact period, UoE research had shown definitively that pneumonia was the largest single cause of childhood mortality globally. UoE researchers produced estimates of global childhood mortality and incidence data related to pneumonia, as well as the first estimates for specific causes of pneumonia such as pneumococcus, Hib, RSV and influenza. This was achieved by applying complex statistical modelling, in-depth literature reviews and leading large international working groups coordinating the structured assembly, analysis and interpretation of unpublished data from LMIC research groups [e.g. 3.1]. This research highlighted, for the first time, the disease burden of pneumonia to policymakers at regional, national and international levels, particularly in LMICs, and influenced WHO, UNICEF and Gavi policies (reported in [REF2014/1/Q](#)).

**New since REF2014: Improved estimates of disease burden and vaccine effectiveness**

Since 2014, the UoE group has continued to conduct and publish research on childhood mortality and pneumonia burden, and has also estimated the major impact of PCV on child pneumonia mortality. The researchers applied new and improved methods to systematically analyse and estimate disease burdens due to child pneumonia overall and due to pneumonia caused by pneumococcus [3.2; 3.4], RSV [3.1] and influenza [3.5] specifically. The pneumonia estimates [3.4] developed by UoE team were used by the International Vaccine Access Center (IVAC) at Johns Hopkins University to jointly develop pneumococcal disease burden estimates [3.2].

Nair and Campbell also developed a new approach using surveillance data to estimate the national burden of influenza pneumonia. This was published in a WHO handbook that they produced [3.6]. As part of the work for the WHO CHERG, Theodoratou estimated the vaccine effectiveness of PCV against radiological pneumonia as 26% [3.3].

At the request of major international agencies determining global policy and investment, including WHO, UNICEF, Gavi and BMGF, UoE researchers have presented these data in various fora, including 6-monthly WHO CHERG and Maternal Child Epidemiology Estimation meetings attended by these agencies, and the Gavi meeting to develop their Vaccine Investment Case for RSV vaccine, to assist agencies in their decision-making.

**Attribution:** Many of the publications listed were based on data shared within large international working groups (of up to 70 LMIC groups), all of which were led by / funded by grants held by the UoE. Campbell, Rudan and Nair led, over a 15-year period, the pneumonia workstream of the WHO / UNICEF CHERG and the pneumonia estimates for the subsequent Maternal and Child Epidemiology Estimation group together with a group from the IVAC at Johns Hopkins University.

**3. References to the research**

[3.1] [Nair H](#), [Nokes DJ](#), [...], [Theodoratou E](#), [...], [Rudan I](#), [Weber MW](#), [Campbell H](#). Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010; 375: 1545-55. doi: [10.1016/S0140-6736\(10\)60206-1](https://doi.org/10.1016/S0140-6736(10)60206-1)

[3.2] [Wahl B](#), [...], [Nair H](#), [McAllister DA](#), [Campbell H](#), [Rudan I](#), [Black R](#), [Knoll MD](#). Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. *Lancet Glob Health*, 2018; 6: e744-e757. doi: [10.1016/S2214-109X\(18\)30247-X](https://doi.org/10.1016/S2214-109X(18)30247-X)

[3.3] [Theodoratou E](#), [Johnson S](#), [Jhass A](#), [Madhi SA](#), [Clark A](#), [Boschi-Pinto C](#), [Bhopal S](#), [Rudan I](#), [Campbell H](#). The effect of *Haemophilus influenzae* type b and pneumococcal conjugate vaccines on childhood pneumonia incidence, severe morbidity and mortality. *Int J Epidemiol* 2010; 39: i172-85. doi: [10.1093/ije/dyq033](https://doi.org/10.1093/ije/dyq033)

[3.4] [Rudan I](#), [O'Brien KL](#), [Nair H](#), [Liu L](#), [Theodoratou E](#), [Qazi S](#), [Lukšić I](#), [Fischer Walker CL](#), [Black RE](#), [Campbell H](#), [Child Health Epidemiology Reference Group \(CHERG\)](#). Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Glob Health* 2013; 3: 010401 doi: [10.7189/jogh.03.010401](https://doi.org/10.7189/jogh.03.010401)

[3.5] [Nair H](#), [Brooks WA](#), [...], [Theodoratou E](#), [...], [Rudan I](#), [Broor S](#), [Simões EAF](#), [Campbell H](#). The global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet*. 2011; 378: 1917-30. doi: [10.1016/S0140-6736\(11\)61051-9](https://doi.org/10.1016/S0140-6736(11)61051-9)

[3.6] [Nair H](#), [Campbell H](#), [Mounts A](#). A manual for estimating disease burden associated with seasonal influenza in a population. WHO document, Geneva 2015, ISBN: 978 92 4 154930 1

**Key grants:**

[3.7] Modelling the impact of emerging interventions against pneumonia (2009–2012), BMGF, USD1,800,000 (GBP1,314,468; 01-21)

[3.8] Improving current global estimates of morbidity and mortality due to RSV–associated acute lower respiratory infections in young children through acquisition of novel data and disease burden modelling (2013–2015), BMGF, USD750,000 (GBP548,677.50; 01-21)

**4. Details of the impact****Continued impact from the REF2014 period: International agency policy**

As reported in [REF2014/1/Q](#), UoE research showing that pneumonia was the largest single cause of global childhood mortality led to high-level policy changes and stakeholder commitments to reduce child pneumonia globally. For example, informed by UoE estimates, in 2009, WHO and UNICEF established the Global Action Plan on Pneumonia, which was updated in April 2013 with the aim to end preventable child deaths from pneumonia and diarrhoea by 2025. Campbell was the lead technical adviser to the UK-led World Health Assembly resolution on the control of child pneumonia in 2010, which was adopted by 190 countries.

The key agencies have continued to use UoE estimates to inform their decisions and programmes since REF2014. Among them, UNICEF continues to play a critical role in supporting the immunisation of children in LMICs through its investment in and support to LMIC governments to expand immunisation programmes globally. The Head of Health at UNICEF noted in 2020: “*CHERG estimates on pneumonia burden of disease have informed UNICEF decisions regarding the need for expansion of coverage of effective interventions, including Hib and pneumococcal conjugate vaccines, against childhood pneumonia.*” [5.1].

Similarly, the Director of Epidemiology at IVAC confirmed in 2020: “*These estimates are used by IVAC as the envelope for the global, regional and national pneumococcal and Hib burden estimates. Professors Nair, Campbell and Rudan have collaborated with IVAC in the development of these estimates. These estimates were (and continue to be) used by WHO, Gavi, and National*

*Ministries of Health to inform policy regarding the introduction of pneumococcal conjugate vaccine's (PCV) in the national immunization programmes."* [5.2].

#### **NEW since REF2014: Impact on accelerating uptake of PCV**

The activities of international agencies and national governments, informed by UoE research as described above, have led to impact on national health policies and investments, which began in the REF2014 period, and have been sustained and expanded in the REF2021 period. As an example, Gavi has prioritised global implementation of pneumonia vaccines, committing USD4,000,000,000 (GBP2,926,440,000; 01-21) to support the cost of pneumococcal vaccines, including PCV, by 2021 [5.3].

By 2013, 38 of the 73 Gavi-eligible countries had introduced PCV. Between 2013 and 2018, this had increased to 60 countries, equating to 80,700,000 additional children with access to PCV [5.3; 5.4a]. The cumulative number of Gavi-eligible countries that have applied for Gavi support for PCV, been approved and have introduced PCV is shown in **Table 1**. This expansion of countries introducing PCV has led to an increase in worldwide PCV coverage from 19% in 2013 to 48% in 2018. A total of 183,000,000 children had been vaccinated by 2018, up from 26,000,000 in 2013 [5.3; 5.4b]. Gavi's Advance Market Commitments report showed that the total number of PCV doses procured by Gavi increased almost 3-fold from 58,000,000 in 2013 to 149,000,000 in 2018 [5.4c].

<b>Cumulative number of countries that have:</b>	<b>2013</b>	<b>2014</b>	<b>2015</b>	<b>2016</b>	<b>2017</b>	<b>2018</b>
Applied for Gavi support for PCV	59	59	59	60	60	61
Been approved	51	55	58	59	59	60
Introduced vaccines	38	46	54	57	58	59
Global PCV coverage	19%	28%	35%	41%	43%	48%
<b>Cumulative number of children vaccinated with Gavi support (in millions)</b>	26	48	76	109	143	183

**Table 1:** Cumulative number of countries that have adopted PCV, showing that PCV uptake and global coverage have accelerated [compiled using figures from 5.3 and 5.4b].

#### **NEW since REF2014: Impact of PCV on children's health and welfare**

While confirmed numbers for 2018–2020 are not yet published, Gavi estimates that 500,000 child deaths have been averted by PCV over the period 2016–2020 [5.5a]. This is supported by Gavi's Advance Market Commitments [5.4d], which states: "*Based on current projections [...] completed in late 2018, PCV use is expected to avert over 700,000 future deaths among children in Gavi-supported countries by 2020*" as well as an analysis published by the UoE group, which observed a reduction in the annual global child pneumonia deaths, from approximately 1,200,000 in 2013 to an estimated 700,000–800,000 in 2020 [5.5b].

#### **NEW since REF2014: Impact on influenza vaccine policy and practice**

In 2015, the UoE group developed a WHO manual to assist countries in making national estimates of influenza disease burden based on national surveillance data [3.6]. This led to estimates that informed national vaccine policy to be made by more than 50 LMICs [5.6a]. In Bhutan this "*directly informed a subsequent national policy decision [in 2018] to adopt a new influenza immunisation program in children nationwide*", as stated by the Head of Bhutan's Department of Public Health. This programme was implemented nationally in 2019 and has achieved over 90% coverage in the target age group [5.6b].

#### **NEW since REF2014: Prioritisation of and investment in RSV vaccines**

UoE researchers' pioneering systematic quantification of the burden of pneumonia disease caused by RSV has led to major international agencies recognising the urgent need for an RSV vaccine, with a senior Medical Officer at the WHO stating: "*Their estimates for RSV-associated child pneumonia informed WHO's [Strategic Advisory Group of Experts] recommendations to WHO for preparatory work required for an RSV vaccine (both with regard to vaccine development and evidence synthesis for introduction of a novel RSV vaccine)*" [5.7]. This has resulted in 3 major, interlinked, developments:



- In 2015, the WHO Product Development for Vaccines Advisory Committee recognised the RSV vaccine as the highest priority future vaccine [5.8]. This resulted in the WHO establishing advisory committees to coordinate and direct international action on vaccine development.
- In November 2018 and April 2019, Gavi prepared a Vaccine Investment Case for RSV for 2021–25, which decided in principle to approve funding for RSV vaccine subject to a future licensed vaccine and WHO pre-qualification being met. UoE's estimates on RSV disease burden were used as the primary data source in this Vaccine Investment Case [5.9a, b].
- The BMGF has invested USD148,233,138 (GBP108,417,717; 01-21) into RSV research since 2010 (when [3.1] was published), of which USD116,382,407 (GBP85,116,273; 01-21) was invested after August 2013 [5.10a], including a USD89,000,000 (GBP65,093,710; 01-21) grant to Novavax in 2015 to develop an RSV vaccine for maternal immunisation to reduce the burden of RSV disease in infants younger than 6 months in LMICs [5.10b]. This investment strategy was directly informed by UoE estimates, with the Pneumonia Director at BMGF confirming these *“aetiology-specific estimates have been a key source of disease burden data that has informed and influenced the Bill and Melinda Gates Foundation in making decisions about investment and priority setting in their programme to control global child pneumonia.”* [5.10c].

As a result of this motivated and coordinated activity to develop an RSV vaccine, there are more than 40 vaccine candidates in development in 2020, compared with none in 2013 [5.11].

### 5. Sources to corroborate the impact

[5.1] Letter of support from Global Solutions Lead for Service Delivery, Health Nutrition and Population (World Bank) and formerly Chief of Health at UNICEF

[5.2] Letter of support from Director of Epidemiology, IVAC

[5.3] [Gavi website describing pneumococcal vaccine support programmes and successes](#)

[5.4] Gavi Advance Market Commitments for pneumococcal vaccines; Annual Report 2018  
a. p.19–20; b. p.7; c. p.14; Fig. 2. d. p. 33

[5.5] Lives saved as a result of increased vaccination coverage

a. [Gavi website showing estimated 500,000 child deaths averted by pneumococcal vaccines](#)

b. Wahl B, O'Brien et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. Lancet Glob Health. 2018 Jul;6(7):e744–e757. doi: 10.1016/S2214-109X(18)30247-X

[5.6] Impact of influenza manual on policy and practice.

a. Letter of support from Director of Global Influenza Programme, WHO, confirming use of UoE's methodology for national influenza burden estimates to inform policy in more than 50 countries.

b. Letter of support from Head of Department of Public Health, Royal Government of Bhutan

[5.7] Letter of support from a senior Medical Officer, Maternal, Neonatal, Child and Adolescent Health programme, WHO

[5.8] Report from WHO Product Development for Vaccines Advisory Committee meeting 2015

[5.9] Evidence that UoE estimates were used as a basis to prepare the evidence base to inform Gavi regarding inclusion of RSV in their Vaccine Investment Strategy (2021–25)

a. Letter of support from Senior Director and RSV Project Lead at PATH Center for Vaccine Innovation and Access

b. Supplementary material in Baral et al. 2020 Vaccine doi: 0.1016/j.vaccine.2020.06.036, listing the experts consulted by Gavi

[5.10] a. List of BMGF grants with the keyword “RSV” 2009–2019. Only grants whose “issue” was given as Pneumonia were counted in the total; b. Details of Novavax grant; c. Letter of support from Director of Pneumonia programme at BMGF

[5.11] Poster by PATH on RSV vaccines in development, March 2020