Institution: University of Warwick

Unit of Assessment: UOA5 - Biological Sciences

Title of case study: Control strategies and policy implementation for respiratory syncytial virus, a global cause of severe pneumonia in childhood

Period when the underpinning research was undertaken: 1 January 2009 - 31 December 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:
Professor James Nokes	Professor of Infectious Diseases	01/10/1995 - present

Period when the claimed impact occurred: 1 August 2013- 31 December 2020

Is this case study continued from a case study submitted in 2014? N

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

Research at the University of Warwick has played a transformative role in initiating the development of a vaccine against respiratory syncytial virus (RSV), the single most important etiologic agent of childhood pneumonia globally. Over 90% of this disease occurs in the poorest nations. Research revealing RSV burden, transmission and optimal vaccination strategies has critically underpinned a multi-stakeholder initiative to drive forward the development of a vaccine for low income settings, changing the policies of the Kenyan Ministry of Health, international non-profit agencies and the World Health Organisation and the development programmes of pharmaceutical companies. In 2020, Warwick research enabled the Kenyan Government to operationalise a rapid response to the COVID-19 pandemic.

2. Underpinning research (indicative maximum 500 words)

Over two decades, research at the University of Warwick has characterised the disease burden, infection dynamics and immune response to respiratory syncytial virus (RSV), with the aim of optimising vaccine control strategies.

What is the burden of disease in the low resource setting?
Denominator-based estimates of disease burden are pre-requisite to national vaccine introduction. Professor Nokes' long-term work in rural Kenya has characterised in fine detail RSV transmission, through intensive hospital and community studies. These studies have become a benchmark for high quality epidemiological research on RSV in low and lower-middle income settings. RSV is revealed as the dominant viral cause of severe hospitalised pneumonia in childhood [3.1], accounting for up to 50% of severe pneumonia admissions during the seasonal outbreaks, leading to heavy demand of hospital resources [3.2]. RSV is particularly prevalent and severe in infancy: Professor Nokes estimated that 1-2 in every 100 new-borns are admitted to hospital with RSV in the first year of life but that the burden of severe RSV disease in the community was 10-fold higher, i.e. 90% of severe RSV cases do not get to hospital for treatment. Nationally, his work estimates some 30,000 RSV associated severe or very severe cases in infants per annum in Kenya [3.2].

Who brings RSV into the home and who infects the infant?
Through intensive monitoring in a household cohort, innovative studies of contacts patterns (using wearable proximity sensors) in household and school settings, and virus genome sequencing, Professor Nokes sought to identify who brings RSV infection into the household and who infects the vulnerable infant. Results show that most household introductions are by elder, mostly school-going, siblings; suggesting schools to be a major source of RSV circulation in the

community [3.3]. In the absence of a vaccine for the very young, this work suggests innovative routes to control transmission and ultimately infection exposure, including family cocoon vaccination (preventing chains of transmission leading to the infant) and school-based intervention (preventing infection getting to the household).

How effectively can maternal immunization protect the infant?
Investigations by Professor Nokes in Kenya evaluated the potential for a maternal vaccine to increase protective antibodies transferred to the infant. This work was funded by PATH, a US non-profit organisation specialising in global health. The level and rate of decay of maternal specific antibody suggested a boosting vaccine would significantly lengthen immune protection in infancy. However, there remain doubts about the immune correlate to use in such studies, which has implications for vaccine manufacturers and trials [3.4].

What are the optimal strategies for RSV vaccine intervention?
Drawing from his extensive epidemiological data from Kenya, a series of mathematical modelling exercises were conducted to explore the potential merits of a range of vaccination strategies for RSV disease prevention. These included delayed infant delivery (since early infant vaccination remains problematic), maternal antibody boosting, school-based campaigns and household cocooning. Research predicted a high impact on the rate of RSV hospitalisation from vaccine delivered to ages 4-10 m (predominantly due to herd immunity which, until then, had not been recognised), and a significant benefit from maternal immunization with or without family cocooning [3.5].

What properties should be enhanced for RSV vaccines?
Using a consensus modelling approach, with the Universities of Oxford and Manchester, Professor Nokes explored the optimal properties of RSV vaccines for GSK biologicals. Results supported enhancing the 'altruistic' properties of their vaccines, i.e. reduce shedding and infectivity of vaccine break-through infections [3.6]. These models were applied in the design of optimal vaccination strategies in both low (Kenya) and high (UK) resource settings.

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

[3.1] Berkley JA, Munywoki P, Ngama M, Kazungu S, Abwao J, Bett A, Lassauniere R, Kresfelder T, Cane PA, Venter M, Scott JA, **Nokes DJ** (2010) Viral etiology of severe pneumonia among Kenyan infants and children. *JAMA* 2010;303(20):2051-7.
[3.2] **Nokes DJ,** Ngama MJ, Bett A, Abwao J, Munywoki P, English M, Scott JAG, Cane PA, **Medley GF** (2009) Incidence and severity of respiratory syncytial virus pneumonia in rural Kenyan children identified through hospital surveillance. Clinical Infectious Diseases 2009;49(9):1341-9.
[3.3] Munywoki PK, Koech DC, Agoti CN, Lewa C, **Cane PA, Medley GF**, **Nokes DJ** (2014) The source of respiratory syncytial virus infection in infants: a household cohort study in rural Kenya. The Journal of Infectious Diseases. 2014;209(11):1685-92.
[3.4] Nyiro JU, Sande CJ, Mutunga M, Kiyuka PK, Munywoki PK, Scott JAG, **Nokes DJ** (2016) Absence of Association between Cord Specific Antibody Levels and Severe Respiratory Syncytial Virus (RSV) Disease in Early Infants: A Case Control Study from Coastal Kenya. PloS ONE. 2016;11(11):e0166706.
[3.5] **Brand SPC**, Munywoki PK, Walumbe D, **Keeling MJ**, **Nokes DJ** (2020) Reducing RSV hospitalisation in a lower-income country by vaccinating mothers-to-be and their households. eLife March 27, 2020 10.7554/eLife.470033.
[3.6] Pan-Ngum W, Kinyanjui T, Kiti M, Taylor S, Toussaint JF, Saralamba S, Van Effelterre T, **Nokes DJ**, White LJ. (2017) Predicting the relative impacts of maternal and neonatal respiratory syncytial virus (RSV) vaccine target product profiles: A consensus modelling approach. Vaccine. 2017;35(2):403-9.

Grants

PI Kevin Marsh (Oxford), Co I James Nokes, Etiology of acute respiratory infection among Kenyan children, Wellcome Trust, December 2006- November 2008, GBP309,625
PI James Nokes, Household transmission of respiratory viruses: who acquires infection from

whom, Wellcome Trust, March 2010- February 2012, GBP297,545
PI James Nokes, The potential impact of vaccination on RSV and other respiratory virus pneumonia in the developing country setting, Wellcome Trust, July 2008- June 2014 GBP1,849,593
PI James Nokes, Quantifying protective immunity correlates for respiratory syncytial virus, PATH Vaccine Solutions 2012-2015 USD374,308
PI James Nokes, Defining pathways of respiratory virus transmission leading to improved intervention strategies, Wellcome Trust, July 2014- June 2020 GBP2,539,908

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

Impact on the global perspective of RSV vaccines for low and middle-income countries
Prior to 2013, there was little focus on RSV vaccine control for low and lower-middle income country (LMIC) settings. The World Health Organisation (WHO) provides global leadership in setting priority areas for research and development for vaccines but had not recognised the gap that existed for RSV.

In 2013, Professor Nokes held discussions with the WHO Initiative for Vaccine Research on the delays or absence of trials of RSV vaccines in LMICs and on the specific need for WHO to promote and broker RSV vaccine availability and affordability in these settings. This catalysed a work stream dedicated to RSV vaccines [5.1]. In response to these discussions, WHO coordinated an international meeting ('Consultation to discuss the conduct of RSV vaccine trials in LMICs and subsequent availability/production of RSV vaccines in LMICs', October 27th 2013) including representatives of the Bill & Melinda Gates Foundation, PATH, National Institutes of Health (part of the US Department of Health and Human Services), and the Wellcome Trust. Subsequent WHO meetings with technical experts, including Professor Nokes, were held in Geneva (2015, 2016) [5.2], and the WHO stated that "these events were instrumental" [5.1] in the publication of the 2017 WHO RSV vaccine ROADMAP [5.3] which lists actions required for the development, licensing and global use of RSV vaccines with emphasis on LMICs. Development and implementation of a vaccine requires coordinated engagement from multiple stakeholders. This important document represents a global commitment to prioritising the development of an RSV vaccine which has played a significant role in driving the engagement of international donor agencies, vaccine manufacturers, and national vaccine programmes.

Professor Nokes contributed directly to global debate as a member of the WHO RSV Vaccine Consultation Expert Advisory Group, providing expert input to the Geneva meetings and the ROADMAP on the progress and challenges in measuring RSV incidence, disease burden, and mortality in LMICs; knowledge gaps requiring future research; on the predicted merits of different strategies for vaccine intervention; and reviewing meeting outputs including publications arising [5.2]. These inputs were based on his experience and research outputs from studies in Kenya.

Establishing global engagement for a vaccine intervention
Research by the University of Warwick is recognised to have elevated awareness of RSV as a major cause of severe pneumonia in childhood in low resource settings, especially sub-Saharan Africa. The Senior Director of the PATH Center for Vaccine Innovation and Access writes: "The Kenya RSV burden, seasonality, and transmission dataset is broadly acknowledged (Bill & Melinda Gates Foundation, WHO, Gavi -the global Vaccine Alliance, RSV small and medium-sized enterprises) as one of the most comprehensive for a (World Bank) lower middle income country" [5.4]. These Kenya data contributed to RSV Global Burden of Disease and Mortality publications which are highly influential in establishing the global and national agendas for vaccine intervention.

The Senior Director PATH attests to the centrality of the research in enabling the development of a vaccine: "The Ministry of Health (Kenya) and population awareness Professor Nokes developed around RSV and the need for prevention is invaluable, aiding acceptance for RSV intervention clinical trials in the country", "Professor Nokes' work has stimulated interest by pharma in conducting vaccine trials and the development of affordable vaccines in LMICs'' [5.4].

Informing and influencing Kenya Ministry of Health public health policy
In 2012, a landscape analysis was conducted by the Nokes research group to inform the Kenya Ministry of Health of RSV burden of disease, associated costs, awareness by key stakeholders, potential interventions, and knowledge gaps [5.5]. In 2018, a stakeholder technical meeting was held, involving representatives from the Kenya National Immunization Technical Advisory Group (KeNITAG), the Ministry of Health National Vaccines and Immunization Progam (NVIP), WHO-Kenya, National Public Health Laboratories, UNICEF, and the Kenya Pediatric Association (KPA) [5.6]. There was a consensus that countrywide studies of RSV burden, seasonality, cost effectiveness and maternal immunisation be undertaken with the aim of identifying the optimal pathway to vaccine introduction. Professor Nokes worked with the Kenya Ministry of Health and KeNITAG to provide evidence to support policy development.

Kenya has a strong record of introducing vaccines to prevent disease, particularly in childhood, as the infectious disease burden is considerable. However due to the logistical and financial hurdles of the stretched healthcare system that a new vaccine creates, alongside there being very little known about RSV, there was no licensed vaccine. The Head of National Vaccines and Immunization Program (NVIP), Ministry of Health, Kenya, leads in developing the national vaccination policy, and strategy for vaccine introduction and implementation. He works closely with vaccine donors such as Gavi and UNICEF and with the World Health Organization's regional and head offices. He writes: "It is now clear, very much from the work of Professor Nokes and his team, that the burden of RSV associated childhood pneumonia in Kenya is high. This awareness has been driven by their long-term community-based burden studies, publications, landscape analysis and technical advisories. We now know that RSV is by far the most important single cause of early childhood severe and life-threatening pneumonia in the country… As a result, the NVIP now has a commitment to engage with Gavi The Vaccine Alliance, a major vaccine donor agency on RSV vaccine introductions, especially now that RSV is on their priority list" [5.7].

Informing RSV vaccine strategies and design
Mathematical models of the potential merits of different vaccine strategies now constitute an integral part of evidence to support decision making by National Immunization Technical Advisory Groups. Professor Nokes' team have published the modelling results of a range of possible options for consideration by the Kenya National Immunization Technical Advisory Group. This is reflected in the recent advisory document on Accelerating Maternal Immunization [5.8].

Foundation for pandemic COVID-19 response in Kenya
The technical capacity and infrastructure developed over 20 years for RSV research by Professor Nokes' team has enabled them to mobilise a rapid, accurate and effective COVID-19 response to support the Ministry of Health (MoH), Government of Kenya. His laboratory at KEMRI-Wellcome Trust established SARS-CoV-2 molecular diagnostics, and is the designated regional testing centre for all coastal Kenya counties. His lab generated the first SARS-CoV-2 genomes, informing the MoH on COVID-19 transmission and the likely impact of early interventions. It is also the national genomics training centre which has trained staff from KEMRI Centres across the country.

Professor Nokes is a member of the National COVID-19 modelling technical committee. His modelling team of Kenyan and Warwick scientists has provided forecasts on the spread of the virus and test intervention scenarios requested by the MoH. The team's research has informed the Government's policy briefs [5.9] which have shaped Kenya's national pandemic response. The KEMRI Centre Director states "the outbreak models produced by Professor Nokes' team informed government decisions in lifting the travel restrictions into and out of the two major cities (Nairobi and Mombasa" [5.10]. The Director also states: "I am confident in saying that the technical excellence of the Nokes team and the infrastructure for investigating respiratory virus pathogens he has established, has substantially underpinned our ability to operationalise a rapid COVID-19 response at the KWTRP… The collaboration between KWTRP and the University of

Warwick, through Nokes, has brought together modelling capability of these institutes that has been applied to forecast the progress of the epidemic and to make predictions of the impact of relaxing or intensifying interventions across the country ''[5.10].

Professor Nokes' long-term contributions to respiratory health in Kenya have been superlative.

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

[5.1] Written statement from WHO representative, Vaccine Product and Delivery Research
[5.2] *Professor Nokes provided expert input to the Geneva meetings and the ROADMAP on the progress and challenges in measuring RSV incidence, disease burden, and mortality in LMICs:* WHO publications from Expert Advisory meetings in Geneva 2015, 2016, (i) Modjarrad K, Giersing B, Kaslow DC, Smith PG, Moorthy VS. WHO consultation on Respiratory Syncytial Virus Vaccine Development Report from a World Health Organization Meeting held on 23-24 March 2015. Vaccine. 2016;34(2):190-7. (ii) Giersing BK, Karron RA, Vekemans J, Kaslow DC, Moorthy VS. Meeting report: WHO consultation on Respiratory Syncytial Virus (RSV) vaccine development, Geneva, 25-26 April 2016. Vaccine. 2017; (iii) Vekemans J, Moorthy V, Giersing B, Friede M, Hombach J, Arora N, et al. Respiratory syncytial virus vaccine research and development: World Health Organization technological roadmap and preferred product characteristics. Vaccine. 2018
[5.3] *The ROADMAP lists actions required for the development, licensing and global use of RSV vaccines with emphasis on LMICs based on University of Warwick research:* World Health Organisation (WHO). RSV Vaccine Research and Development Technology ROADMAP. 2017.
[5.4] Written statement from PATH Senior Director
[5.5] *In 2012 a landscape analysis to inform the Kenya Ministry of Health of RSV burden of disease, associated costs, awareness by key stakeholders, potential interventions, and knowledge gaps:* Gravel G. The use of a pediatric prophylactic vaccine for respiratory syncytial virus in Kenya. KEMRI-Wellcome Trust, Kenya and University of Warwick, UK; 2012
[5.6] *There was a consensus that the stakeholders continue to be updated, that countrywide studies of RSV burden, seasonality, and cost effectiveness be undertaken, and that implementation research be undertaken to support RSV maternal immunization:* Stakeholder's Technical Meeting Report: Epidemiology and control options of respiratory syncytial virus (RSV) in the Kenyan context, KEMRI HQ, 17th September 2018
[5.7] Written statement from Head National Vaccine and Immunization Program, MoH, Kenya.
[5.8] *Professor Nokes promoted Objective 7 'Conduct modelling to examine the effect of alternative delivery strategies on maternal RSV vaccine impact and cost-effectiveness':* PATH Advancing RSV Maternal Immunization: A Gap Analysis Report; PATH A Roadmap for Advancing RSV Maternal Imunization, Center for Vaccine Innovation and Access, PATH October 2018.
[5.9] KEMRI-Wellcome Trust Policy Briefs, March 2020, What can we learn from preliminary modelling of COVID-19 in Kenya?; KEMRI-Wellcome Trust Policy Brief, 01/06/2020, Genome sequencing of SARS-CoV-2 cases in Kenya; KERMI-Wellcome Trust Policy Brief, 25/08/2020., Status of the COVID-19 Pandemic in Kenya: Evidence from serological and clinical surveillance, and predictive modelling; KEMRI-Wellcome Trust Policy Brief, 26/10/2020. Status of the COVID-19 pandemic in Kenya: Evidence from national case-based surveillance, serosurveillance and hospital-based clinical surveillance
[5.10] Written statement from Centre Director KEMRI