Institution: Queen's University Belfast

Unit of Assessment: 1

Title of case study: Debunking MMR vaccine associated scares.

1. Summary of the impact

Professor Rima's research on measles and mumps viruses over 4 decades at Queen's University allowed him to play an important role in re-establishing public confidence in the safety of the measles-mumps-rubella (MMR) vaccine. Claims that MMR vaccine could cause autism in 1998 undermined the vaccine uptake but Rima's expert testimony and that of others established in court that these claims were unfounded. This re-assurance and subsequent promotion of MMR vaccination reduced measles cases in the UK. In the USA, it also reduced the real risk that the Vaccine Court Fund, which compensates vaccinees for genuine vaccine related adverse events, would be bankrupted by over 50,000 claims amounting to between $30-50 Billion.

2. Underpinning research

Publications that cast doubt on the safety of the MMR vaccine led to reduced vaccination rates resulting in measles outbreaks with fatal cases in the UK and Ireland. Rima's research on measles and mumps virus has led to over 170 peer reviewed research publications and invited reviews, and has been funded by the major UK funding agencies such as the Wellcome Trust and all relevant UK Research Councils. His work focussed on the application of molecular biology to these viruses. His research on the genetics of these viruses provided the groundwork for the work of relevance to this impact case study. The delineation of genetic differences between vaccine and wild type viruses[1,2] was particularly relevant. Wakefield claimed in 1992 that measles virus was involved in inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis. After 1992 the claim shifted from an involvement of "street" or wild-type measles virus to involvement of "vaccine" measles. Rima's research insights in distinguishing the vaccine from circulating wild type virus were crucial in refuting Wakefield's claims. In the case of measles virus, all vaccines are derived from viruses with a specific genetic signature (genotype A), which appeared to be extinct in the wild (i.e. was no longer isolated) with all "street" viruses belonging to other genotypes. This allowed for easy distinction between cases apparently derived from vaccine virus or wild type virus. The ability to make this distinction became even more important when Wakefield published his 1998 claim that there was a link between the measles component in MMR vaccine and autism. This claim by Wakefield was largely based on the "findings" by Dr John O'Leary's laboratory in Dublin of measles vaccine virus genetic material in gut biopsies of children with autism long after vaccination. This brought into play the question of persistence of the virus in human tissue.
Rima and colleagues at Queen's University had extensive experience before and after 1992 in dealing with claims of the presence of measles and related canine distemper virus in diseases such as Paget's disease[3], otosclerosis and multiple sclerosis. The same applied to mumps virus in inclusion body myositis and other diseases for which claims for paramyxovirus involvement had been made. None of these claims were sustained when sequence analyses of the genetic material of the viruses found in the cases were performed. This demonstrated that the measles genetic material detected was largely due to sample contamination with cloned viral DNA sequences. The difficulty in these cases and in all diseases for which a causative role for a specific virus is claimed is that it is impossible formally to prove the absence of something like a virus. Hence, the question is always decided on the basis of demonstrations of technical flaws in the evidence or direct evidence of contamination of the samples[3]. Insights gained from Rima's studies on persistent infections by measles virus *in vivo* and *in vitro*[4,5] and the understanding of the evolution of viruses[6] during normal circulation and persistent infection was crucial for evaluating the validity of Wakefield's claims about MMR vaccine and autism.

In summary, Rima's work was crucial in demonstrating the flawed nature of the only positive "evidence" provided by Wakefield and his supporters, which was detection of viral RNA in the children.

3. References to the research

1 Yeo, R.P., Afzal, M.A., Forsey, T. & Rima, B.K. (1993). Identification of a new mumps virus lineage by nucleotide sequence analysis of the SH genes of ten different strains. Archives of Virology 128, 371-377 (*47 citations; first identification of genome area that can be used for genotyping of mumps virus strains; still primary area in use*).

2 Rima, B.K., Earle, J.A.P., Yeo, R.P., Herlihy, L., Baczko, K., ter Meulen, V., Carabaña, J., Caballero, M., Celma, M.L. & Fernandez-Muñoz, R. (1995). Temporal and geographical distribution of measles virus genotypes. Journal of General Virology, 76, 1173-1180 (*113 citations; identification of genome area that can be used for genotyping of strains; still primary area in use; first demonstration of temporal and geographic distribution of measles virus strains)*.

3 Stuart H Ralston, Miep H Helfrich, Muhammad Afzal, Jim Gallagher, William D Fraser, Andrew Mee and Bert Rima (2007). Multicenter blinded analysis of RT-PCR detection methods for paramyxoviruses in relation to Paget's disease of bone. J Bone Min Res. 22(4), 569-77 *(22 citations; a multicentre study led by Rima to assess interlaboratory variations in sensitivity of technique, in all but one (US) laboratories that had claimed a role for measles and canine distemper virus in Paget's disease)*.

4 Backzo, K., Lampe, J., Liebert, U.G., ter Meulen, V., Pardowitz, I., Budka, H., Cosby, S.L., Isserte, S. & Rima, B.K. (1993). Clonal expansion of hypermutated measles virus in an SSPE brain. Virology 197, 188-195 (86 citations; study on the nature of persistent virus in the CNS).

5 Rima, B.K. and Duprex W.P. (2005). Molecular mechanisms of measles virus persistence. Virus Research 111, 132-147 *(47 citations review)*.

6 Rima, B.K., Earle, J.A.P., Baczko, K., ter Meulen, V., Liebert, U.G., Carstens, S.C., Carabaña, J., Caballero, M., Celma, M.L. & Fernandes-Muñoz, R. (1997). Sequence divergence of measles virus haemagglutinin during natural evolution and adaptation to cell culture. Journal of General Virology 78, 97-106 *(139 citations; study on the evolution of measles virus)*.

Funding:
1992-1995 **Wellcome Trust:** Expression of mumps virus polypeptides with the objective of rescuing virus from an infectious cDNA clone (£88,279).

1996-1999 **Wellcome** Trust: Grant in collaboration with Dr S.L. Cosby.
Reverse genetic approaches to the study of measles virus neurovirulence and attenuation (£125,296).

1997-2000 **BBSRC**: Grant in collaboration with Dr T. Barrett (IAH, Pirbright). Pathogenesis, cross-species infectivity and immunogenicity of morbilliviruses (£210,000).

2000-2002 **NARPD:** Grant with Prof S Ralston (Aberdeen); scientific co-ordination in Belfast. Paramyxoviruses and Paget's disease; a multicentre comparison of PCR methods for detecting viral transcripts (£19,000).

2001-2006 **MRC**: Programme grant in collaboration with Drs Cosby and Duprex. Linking measles virus genotypes to phenotypes (£549,000).

2005-2008 **Wellcome Trust**: Showcase award with Dr Paul Duprex. Persistently addressing persisting problems: persistent infections as possible solutions (£125,000)

2003-2008 **Wellcome Trust:** Project grant with Drs. Duprex and Cosby. Neurovirulence and attenuation of mumps virus. (£418,000)

2006-2010 **MRC:** Programme grant with Dr Duprex: The role of translational control in the natural history of measles virus (£633,184).

2008-2012 **MRC:** Models grant with Dr Paul Duprex and Rotterdam Erasmus University group. Re: G0801001 - Illuminating childhood respiratory infections: from viral diseases to vaccine delivery (£900,000).

4. Details of the impact

Rima's knowledge of measles and mumps vaccine viruses made him the ideal expert witness in two major court cases in the UK pre 2004 and in the US from 2007 to 2009 to deal with claims of adverse reactions to MMR vaccine[1]. At a Medical Research Council hearing in 1998, Rima and other scientists demonstrated flaws in Wakefield's claimed link between measles vaccine and IBD. Wakefield's 1998 claim for a causative link between MMR vaccine and autism led to widespread media coverage, public alarm, and a reduction in MMR uptake[2] with consequences still apparent today as the UK suffers unnecessary outbreaks of measles and mumps .
Parents of children with autism in the UK sued three major vaccine manufacturers potentially claiming over £3 Billion in compensation. Seven test cases were selected. Many reports were furnished by a great number of experts in the UK focussing on every aspect of the test cases including the validity of the diagnosis and timings between onset of symptoms and vaccination. However, the only direct and positive evidence was the detection of measles vaccine RNA sequences in gut biopsies from the children by O'Leary's company Unigenetics Ltd in Dublin acting on behalf of the claimants. They claimed to have detected measles vaccine by three techniques; two of which (*in situ* hybridisation and RT-PCR) are standard techniques with which Rima had experience for measles and mumps and a third test (allelic exclusion technology) developed by O'Leary for distinguishing vaccine from wild-type virus. However, RNA sequence evidence that could have been obtained from the RT-PCR tests and which could unambiguously distinguish vaccine from wild type virus was never presented by the claimant's experts, though requested repeatedly by Rima.

Confidential expert reports from Simmonds (Edinburgh) and Rima on the direct evidence for the presence of viral RNA successfully identified flaws in the data and its analysis. An expert report from Professor Bustin, an expert in quantitative RNA detection at University College London also pointed to flaws in the O'Leary application of the technology and the data. Rima also demonstrated that the third test developed by O'Leary was unreliable and that their results were misinterpreted even according to their own flawed criteria[3,4].

The scientific evidence was not tested in open court in the UK. This allowed the claimants to proclaim a "cover up" and allowed Wakefield to start an anti-MMR campaign in the US, again using O'Leary's laboratory data and to claim that measles vaccine RNA had been detected in children with autism. US vaccine manufacturers pay a per-dose-levy to a compensation fund for genuine vaccine-related adverse events. Such cases are adjudicated by the Vaccine Court. Three US test cases were considered in this court and several UK and US experts testified in the three test cases. Only Bustin and Rima's redacted reports[3] from the UK litigation were used, as it was clear that the direct "evidence" for the presence of measles virus in the children would be decisive in allowing the court to decide the validity of the claims. Bustin's report identified technical flaws in the RNA detection technique used by O'Leary, highlighted potential sources of contamination and pointed to an altered lab book entry (also noted by Rima[1,3,4]).

Rima testified in front of Special Master Denise Vowell, the federal judge in the vaccine court in the Colten Snyder test case. In 2008, affidavits supplied by the claimants to discredit Rima's evidence were successfully answered and rebutted leading to the publication of final judgments in 2009. Judge Vowell and her co-jurists commented that: "Doctor Rima was a superb expert witness. He was well-qualified in the subject matter of his testimony, testified directly and forthrightly, and made extremely difficult topics understandable. He made his disapproval of certain laboratory practices perfectly plain, without engaging in *ad hominem* attacks"[5,6,7,8]. Her judgement stated[5]:
"After careful consideration of all of the evidence, it was abundantly clear that petitioners' theories of causation were *speculative and unpersuasive*. Respondent's experts were far more qualified, better supported by the weight of scientific research and authority, and simply more persuasive on nearly every point in contention. *Because of pervasive quality control problems at a now-defunct laboratory that tested a key piece of evidence, petitioners could not reliably demonstrate the presence of a persistent measles virus in Colten Snyder's central nervous system*".

This protected the National Vaccine Injury Compensation Program fund from claims that would

have exhausted it completely. This judgement as well as many other epidemiological studies and reports renewed confidence in the MMR vaccine leading to a change in uptake in the UK, for example, from below 80% in 2003, to about 85% in 2008 and 91% currently[9,10].

The recent outbreak in Swansea in 2013 highlights the disastrous impact that Wakefield and O'Leary's MMR claims have had. If the direct evidence for measles genetic material in the affected children had not been refuted, measles fatalities such as the two in the Yorkshire outbreak in 2008 and the one fatality in South Wales would have been repeated time and time again. We also would continue to have the large number of hospitalisations for pneumonia in 15-20% of the affected children and the spectre of long queues at emergency vaccination clinics of the several hundred thousand children not vaccinated as a result of this affair. Many people played in important roles in showing the false nature of the claimed link between autism and MMR vaccination, but if the direct evidence from Unigenetics Ltd had remained unchallenged it would have been highly unlikely that confidence in the vaccine could have been restored.

5. Sources to corroborate the impact

1 *Lead consultant at Hogan Lovells International LLP, Atlantic House , Holborn Viaduct, London EC1A 2FG.*
2 *Impact of Wakefield's claims: http://briandeer.com/mmr/uptake-stats.htm*
3 *Rima's expert report: This is a **confidential** redacted expert report from the UK confidential to the US court and an affidavit for the US cases*
4 *http://www.uscfc.uscourts.gov/sites/default/files/autism/OmnibusTrialsTranscripts/snyder/20071108_snyder_pps820-1014.pdf*
5 *http://www.uscfc.uscourts.gov/sites/default/files/vaccine_files/Vowell.Snyder.pdf page 17*
6 *http://www.uscfc.uscourts.gov/sites/default/files/vaccine_files/Hastings-Cedillo.pdf page 52*
7 *http://www.uscfc.uscourts.gov/sites/default/files/Hazlehurst.pdf page 17*
8 *Email from US Department of Justice.*
9 *http://www.hpa.org.uk/NewsCentre/NationalPressReleases/2011PressReleases/110624Measlesstatement/*
10 *https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/192611/Presentation_by_Mary_Ramsay_-_Measles_in_England_2012___2013.pdf*