Cost-Effectiveness of Rubella Vaccination: Informing Implementation in South Africa

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INTRO

- Rubella is a contagious viral infection with a high prevalence in young children in South Africa; rubella-containing vaccines (RCVs) are available in private but not public health system
- Symptomatic rubella rarely causes severe morbidity in infants or adults…. main concern relates to infection during pregnancy. Severe complications (e.g., deafness, encephalitis) caused by congenital rubella syndrome (CRS)
- Vaccination programmes aim to either reduce incidence of CRS through immunization of young children and women of childbearing age or eliminate rubella through immunization of a wider population
- Objectives: (i) Review literature pertaining to cost-effectiveness of RCV programmes with focus on existent literature which employed dynamic decision models for analysis, (ii) Assess future research required to inform RCV implementation in South Africa

DYNAMIC MODELLING OF RUBELLA

- If sufficient coverage is not achieved with an RCV, an increase in CRS incidence may occur, resulting from a reduction in circulating rubella amongst children following introduction of the vaccine, such that individuals reach childbearing age without being exposed to the virus
- 'Dynamic' models are required to properly predict effectiveness of interventions affected by interaction between infective and susceptible individuals… 'Static' models (e.g., decision trees, Markov models) cannot capture these effects
- Metcalf et al. (1) developed a dynamic 'susceptible-infective-recovered' (SIR) model which assesses minimum RCV coverage to avoid increase in CRS
- Given South Africa's birth rate (~20/1,000), estimates of rubella disease transmission intensity (R_0=6-9), this analysis was used to derive minimum required coverage to avoid increase in CRS based on routine immunization, routine immunization plus supplementary immunization activities (SIAs) for 1 to 4 year-olds every four years, or routine immunization plus SIAs for 1 to 14 year-olds every four years (Table 1) – these results align with central estimates from a South Africa-specific dynamic modelling study
- South African National Department of Health estimates coverage of 78% for measles vaccine, while WHO & UNICEF estimate 60% (2)

METHODS

1. PubMed and Web of Science 2013-2019 searched using terms: ("rubella" AND "economics") OR ("rubella" AND "cost") OR ("CRS" and "economics") OR ("CRS" and "cost")
2. Inclusion criteria: cost-benefit, cost-effectiveness, and/or cost-utility analyses, analysis of RCV programme
3. Titles read in first review, abstracts read in second review, full article read in third review, with exclusion – based on increasing sensitivity – occurring after each review; results supplemented with studies identified in two previous systematic reviews of rubella infection (3,4)
4. Methods, key findings, setting, perspective, vaccination strategies, and type of analysis extracted from reviewed articles

RESULTS

- N=288 studies identified, N=7 included for full reading after title and abstract review (171 not correct type of study, 72 not about rubella), N= 4 included for final review, alongside N=14 from previous systematic reviews
- Summaries in Table 2: only 2 cost-utility analyses, which capture morbidity and mortality and allow for comparison with other investments in health, have been conducted of RCVs, one Japanese study (Saito, 2018) used a dynamic SIR model, but did not consider health utility or potential increases in CRS

DISCUSSION & FURTHER WORK

- Many cost-benefit and cost-effectiveness analyses of RCVs have been conducted, and these generally support some form of RCV implementation
- No cost-utility analysis has been conducted with a dynamic model
- …ongoing work will assess cost-effectiveness of different RCV implementation strategies in South Africa with dynamic SIR model, accounting for potential increases in CRS and costs associated with different strategies

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There is a lack of cost-utility analyses of rubella-containing vaccinations and existing economic evaluations **employ static decision models which are unable to predict increases in congenital rubella syndrome** attributable to low vaccine coverage

immunizationeconomics.org/baselposter/kohlilynch

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1. Metcalf, C. J. E., et al. "Impact of Birth Rate, Seasonality and Transmission Rate on Minimum Levels of Coverage Needed for Rubella Vaccination." Epidemiology and Infection, vol. 140, no. 12, 2012, pp. 2290–2301.
2. WHO, UNICEF. South Africa: WHO and UNICEF estimates of national immunization coverage: 2017 revision. World Health Organization and the United Nations Children's Fund; 2018.
3. Hinman, A.R., et al. "Economic analyses of rubella and rubella vaccines: a global review." Bulletin of the World Health Organization, vol. 80, no. 4, 2002, pp. 264-70.
4. Babigumira, Joseph B, et al. "Health Economics of Rubella: a Systematic Review to Assess the Value of Rubella Vaccination." BMC Public Health, vol. 13, no. 1, 2013.

Table 1: Sufficient RCV coverage rate to avoid increase in CRS due to increased age of rubella contraction, adapted from Metcalf et al.

	Transmission Intensity	
Strategy	R_0 = 8	R_0 = 12
Routine immunization	23%	57%
Routine immunization + SIA of 1-4 year-olds	11%	34%
Routine immunization + SIA of 1-14 year-olds	10%	34%

Table 2: Summaries of cost-benefit, cost-effectiveness, and cost-utility studies reviewed

Reference	Country	Method	Study Type	Notes/Findings
Identified in previous reviews (n=14)				
Schoenbaum et al. (1976)	USA	Micro-costing	CBA	Outcome: Benefit-cost ratio (benefits: averted costs) Perspective: Societal Vaccination strategies (lifetime horizon): A. All 2 year-olds B. All 6 year-olds C. All 12 year-olds D. 2 year-olds and 12 year-olds Findings: Vaccination at 12 has higher BCR (3.27) than age 6 (2.9) or 2 (1.8), Strategy D had best CBR (4.8)
Chapalain et al. (1978)	France	Micro-costing & primary data analysis	CEA	Outcome: Cost/LYS Perspective: Health sector Vaccination strategies (15 year time horizon): A. No vaccination B. Vaccinate 13 year-olds and women Findings: cost/LYS of vaccination programme – $13,300/LYS (USD2019
Elo et al. (1979)	Finland	Delphi panel	CBA	Outcome: Benefit-cost ratio (benefits: averted costs) Perspective: Societal A. Vaccination strategies (30 year time horizon): B. 13 year-old girls & post-partum women C. 13 year-old girls & 1 year-old girls D. Only 1 year-old girls over period of 20 years Findings: Highest benefit-cost ratio achieved by vaccinating 13 year-old girls (CBR: 10, Strat' C – 6, Strat' B – 3)
Stray-Pedersen et al. (1982)	Norway	Micro-costing	CBA	Outcome: Benefit-cost ratio (benefits: averted costs) Perspective: Societal Vaccination strategies (lifetime horizon): A. Infant girls B. Pubertal girls Findings: Vaccination of pubertal girls preferable to infant girls (BCR: 2.11 vs. 1.5)
Golden et al. (1984)	Israel	Micro-costing	CBA	Outcome: Benefit-cost ratio (benefits: averted costs) Perspective: Societal Vaccination strategies (10 year time horizon): A. Vaccinate all pre-pubertal children B. Vaccinate children between ages 12 and 14 C. Vaccinate all adult females Findings: CBR above 1 for Strategy B, unclear for Strategy A, and below 1 for Strategy C.
White et al. (1985)	USA	Micro-costing	CBA	Outcome: Benefit-cost ratio (benefits: averted costs) Perspective: Societal Vaccination strategies (lifetime horizon): A. Childhood rubella vaccination B. Childhood MMR vaccination Findings: High CBR for both vaccinations programmes, higher BCR for MMR (14.4 vs. 7.7)
Bjerregaard et al. (1991)	Denmark	Micro-costing	CBA	Outcome: Benefit-cost ratio (benefits: averted costs) Perspective: Societal Vaccination strategies (20 year time horizon): A. 15 month-olds & 12 year-olds B. Only 15 month-olds Findings: Vaccination of both groups preferable to only 15 month-olds (BCR: 3 vs. 2)
Hatzandrieu et al. (1994)	USA	Micro-costing	CBA	Outcome: Benefit-cost ratio (benefits: averted costs) Perspective: Societal Vaccination strategies (lifetime horizon): A. Childhood rubella vaccination B. Childhood MMR vaccination Findings: High CBR for both vaccinations programmes, higher BCR for MMR (21.1 vs. 11.1)
Kommu et al. (1997)	Barbados	NC*	CBA	Outcome: Benefit-cost ratio (benefits: averted costs) Perspective: NC* Vaccination strategies (15 year time horizon): A. No vaccination B. Rubella eradication programme with MMR vaccination Findings: eradication programme BCR: 4.6
Kandola et al. (1998)	Guyana	NC*	CEA	Outcome: Cost/CRS case prevented Perspective: NC* Vaccination strategies (5 year time horizon): A. No vaccination B. Rubella eradication programme Findings: eradication programme costs ~$2,600/CRS case prevented (USD 2019)
Irons et al. (2000)	Caribbean	NC***	CBA	Outcome: Benefit-cost ratio (benefit: averted costs) and cost/CRS case prevented Perspective: NC*** Vaccination strategies (20 year time horizon): A. No vaccination B. Rubella interruption programme in the English-speaking Caribbean Findings: BCR – 13.3, cost/CRS case prevented – $4,310 (USD 2019)
Hudeckova et al. (2001)	Slovakia	NC**	CEA	Outcome: Cost/CRS case prevented Perspective: Health sector Vaccination strategies (time horizon: NC**): A. 1996 Slovakian MMR vaccination campaign B. No vaccination campaign Findings: programme cost ~$340/CRS case prevented (USD 2019)
Zhou et la. (2004)	USA	Micro-costing and DT	CEA	Outcome: Cost/CRS case prevented, cost/LYS Perspective: Societal Vaccination strategies (40 year time horizon): A. 2-dose MMR vaccination, initiated 1989 B. No vaccination campaign Findings: programme saves lives and prevents CRS cases compared to no vaccination programme
Lugner et al. (2010)	NL	Static WBM	CUA	Outcome: Cost/QALY Perspective: Health sector Vaccination strategies (16 year time horizon): A. Screen & vaccinate unvaccinated women in LVRs B. Screen & vaccinate pregnant women in LVRs C. Screen & vaccinate all unvaccinated women in NL Findings: Strategy A dominated Strategy B. Strategy C had high ICER ($120,400/QALY USD 2019). Results very sensitive to: willingness to vaccinate in LVR, at least 1 rubella epidemic during 16 year period
Identified in updated review (n=4)				
Straub et al. (2013)****	Texas	DT	CUA	Outcome: average cost/QALY Perspective: Health sector Vaccination strategies (lifetime horizon): A. Universal rubella screening and vaccination B. Screening and vaccination if previous titer not available Electronic medical records alert to prompt screening and vaccination Findings: Universal screening most cost costly and most effective, incremental cost-effectiveness ratio could not be calculated – average CER for universal screening $2.29/QALY, screen if previous titer not available $2.20/QALY, EMR alert $0.27/QALY, note average CER
Zhou et al. (2014)	USA	DT	CBA	Outcome: cost/rubella case prevented, cost/CRS case prevented, cost/death prevent Perspective: Health sector and societal Vaccination strategies (lifetime horizon): A. No vaccination B. Routine immunization of 2009 U.S. birth cohort Findings: Cost savings per rubella case, CRS case, and death prevented (both perspectives)
Ozawa et al. (2017)	73 LMICs	DT	CEA CUA	Outcome: cost/death prevent, cost/cases prevented, cost/long-term disability prevented, cost/acute disease hospitalisations prevented, cost/DALY averted Perspective: Health sector and societal Vaccination strategies (lifetime horizon): A. No vaccination B. Forecasted coverage rates for rubella vaccination in 73 low- and middle-income countries (2001-2020 and 2011-2020) Findings: Cost savings achieved with positive health benefits for all metrics considered (both perspectives, 2001-2020 and 2011-2020)
Saito et al. (2018)	Japan	DYN-SIR	CBA	Outcome: cumulative incidence of rubella, benefit-cost ratio (benefits: averted costs) - both presented as function of proportion immune before supplementary vaccination) Perspective: Societal Vaccination strategies (lifetime horizon), both considered with fixed number of available vaccines: A. Random vaccination of x% of population B. Test and vaccinate x% of population Findings: Test and vaccinate strategy marginally better than random vaccination at reducing cumulative incidence of rubella, but benefit-cost ratio consistently better for random allocation

BCR – benefit-cost ratio, CBA – cost-benefit analysis, CEA ¬¬– cost-effectiveness analysis, CER ¬– cost-effectiveness ratio, CRS ¬– congenital rubella syndrome, CUA – cost-utility analysis, DT – decision tree, DYN-SIR – dynamic susceptible-infective-recovered, EMR – electronic medical records, FF – French Francs, LMICS – Low- and middle-income countries, LVR – low vaccination regions, LYS – life year saved, MMR – measles mumps rubella, NC – not clear, NL – Netherlands, WBM – worksheet-based model
*Reported in the Pan-American Health Organisation's final report of English-Speaking Caribbean EPI Managers meeting 1997 **Article could not be accessed, data only available from abstract and previous systematic reviews ***Summary data from unavailable Pan-American Health Organisation's final report of English-Speaking Caribbean EPI Managers ****Severely limited study methodology – estimation of average, not incremental, cost-effectiveness ratio