VACCINE DELIVERY RESEARCH DIGEST

UNIVERSITY OF WASHINGTON GLOBAL HEALTH START PROGRAM
REPORT TO THE BILL AND MELINDA GATES FOUNDATION

JULY 15, 2015

PRODUCED BY: FARLEY JM, DUERR A
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1. PNEUMONIA PREVENTION DURING A HUMANITARIAN EMERGENCY: COST-EFFECTIVENESS OF HAEMOPHILUS INFLUENZAE TYPE B CONJUGATE VACCINE AND PNEUMOCOCCAL CONJUGATE VACCINE IN SOMALIA.

Gargano LM, Hajjeh R, Cookson ST.
Prehosp Disaster Med. 2015 June 10:1-10. [Epub ahead of print].
PMID: 26061190

ABSTRACT

BACKGROUND: Pneumonia is a leading cause of death among children less than five years old during humanitarian emergencies. Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae are the leading causes of bacterial pneumonia. Vaccines for both of these pathogens are available to prevent pneumonia.

PROBLEM: This study describes an economic analysis from a publicly funded health care system perspective performed on a birth cohort in Somalia, a country that has experienced a protracted humanitarian emergency.

METHODS: An impact and cost-effectiveness analysis was performed comparing: no vaccine, Hib vaccine only, pneumococcal conjugate vaccine 10 (PCV10) only, and both together administered through supplemental immunization activities (SIAs). The main summary measure was the incremental cost per disability-adjusted life-years (DALYs) averted. One-way sensitivity analysis was conducted for uncertainty in parameter values.

RESULTS: Each SIA would avert a substantial number of cases and deaths. Compared with no vaccine, the DALYs averted by two SIAs for two doses of Hib vaccine was US $202.93 (lower and upper limits: $121.80-$623.52), two doses of PCV10 was US $161.51 ($107.24-$227.21), and two doses of both vaccines was US $152.42 ($101.20-$214.42). Variables that influenced the cost-effectiveness for each strategy most substantially were vaccine effectiveness, case fatality rates (CFRs), and disease burden.

CONCLUSIONS: The World Health Organization (WHO) defines a cost-effective intervention as costing one to three times the per capita gross domestic product (GDP; in 2011, for Somalia=US $112). Based on the presented model, Hib vaccine alone, PCV10 alone, or Hib vaccine and PCV10 given together in SIAs are cost-effective interventions in Somalia. The WHO/Strategic Advisory Group of Experts decision-making factors for vaccine deployment appear to have all been met: the disease burden is large, the vaccine-related risk is low, prevention in this setting is more feasible than treatment, the vaccine duration probably is sufficient for the vulnerable period of the child's life, cost is reasonable, and herd immunity is possible.

WEB: http://dx.doi.org/10.1017/S1049023X15004781

IMPACT FACTOR: 0.00
CITED HALF-LIFE: 0.00
UW EDITORIAL COMMENT: Table 3 shows the impact of Hib and PCV10 Vaccination Program on Total Pneumonia Events in Somalia during 2012.
2. OPTIMIZING NATIONAL IMMUNIZATION PROGRAM SUPPLY CHAIN MANAGEMENT IN THAILAND: AN ECONOMIC ANALYSIS.

Riewpaiboon A, Sooksriwong C, Chaiyakunapruk N, Tharmaphornpilas P, Techathawat S, Rookkapan K et al.

Public Health. 2015 May 28. pii:S0033-3506(15)00190-0. [Epub ahead of print].
PMID: 26027451

ABSTRACT

OBJECTIVES: This study aimed to conduct an economic analysis of the transition of the conventional vaccine supply and logistics systems to the vendor managed inventory (VMI) system in Thailand.

STUDY DESIGN: Cost analysis of health care program.

METHODS: An ingredients based approach was used to design the survey and collect data for an economic analysis of the immunization supply and logistics systems covering procurement, storage and distribution of vaccines from the central level to the lowest level of vaccine administration facility. Costs were presented in 2010 US dollar.

RESULTS: The total cost of the vaccination program including cost of vaccine procured and logistics under the conventional system was US$0.60 per packed volume procured (cm3) and US$1.35 per dose procured compared to US$0.66 per packed volume procured (cm3) and US$1.43 per dose procured under the VMI system. However, the findings revealed that the transition to the VMI system and outsourcing of the supply chain system reduced the cost of immunization program at US$6.6 million per year because of reduction of un-opened vaccine wastage.

CONCLUSIONS: The findings demonstrated that the new supply chain system would result in efficiency improvement and potential savings to the immunization program compared to the conventional system.

WEB: http://dx.doi.org/10.1016/j.puhe.2015.04.016

IMPACT FACTOR: 1.43

CITED HALF-LIFE: 0.00

UW EDITORIAL COMMENT: This study addresses a gap in the literature; it is the first known study in Asia to create an empirical evidence base for the economic benefits of vendor-managed inventory (VMI). The finding that this supply chain system saves money is attributed to two likely factors. First, the VMI system prevents un-opened vial wastage, therefore leading to lower procurement amounts and costs. Second, logistical costs are reduced by using more sophisticated IT applications and cutting out intermediate warehouses. Table 2 displays logistics costs at the facility level for the conventional and VMI system, while Table 3 shows a comparison of outputs and costs between the conventional and VMI system.
3. INTRODUCTION OF A NATIONAL HPV VACCINATION PROGRAM INTO BHUTAN.

Dorji T, Tshomo U, Phuntsho S, Tamang TD, Tshokey T, Baussano I et al.
PMID: 26057136

ABSTRACT

BACKGROUND: Cervical cancer is the most common cancer in Bhutanese women. To help prevent the disease, the Ministry of Health (MoH) developed a national human papillomavirus (HPV) vaccine program.

METHODS: MoH considerations included disease incidence, the limited reach of cervical screening, poor outcomes associated with late diagnosis of the disease, and Bhutan’s ability to conduct the program. For national introduction, it was decided to implement routine immunization for 12 year-old girls with the quadrivalent HPV6/11/16/18 (QHPV) vaccine and a one-time catch-up campaign for 13-18 year-old girls in the first year of the program (2010). Health workers would administer the vaccine in schools, with out-of-school girls to receive the vaccine at health facilities. From 2011, HPV vaccination would enter into the routine immunization schedule using health-center delivery.

RESULTS: During the initial campaign in 2010, over 130,000 doses of QHPV were administered and QHPV 3-dose vaccination coverage was estimated to be around 99% among 12 year-olds and 89% among 13-18 year-olds. QHPV vaccine was well tolerated and no severe adverse events were reported. In the three following years, QHPV vaccine was administered routinely to 12 year-olds primarily through health centers instead of schools, during which time the population-level 3-dose coverage decreased to 67-69%, an estimate which was confirmed by individual-level survey data in 2012 (73%). In 2014, when HPV delivery was switched back to schools, 3-dose coverage rose again above 90%.

DISCUSSION: The rapid implementation and high coverage of the national HPV vaccine program in Bhutan were largely attributable to the strength of political commitment, primary healthcare and support from the education system. School-based delivery appeared clearly superior to health centers in achieving high-coverage among 12 year-olds.

CONCLUSIONS: Bhutan’s lessons for other low/middle-income countries include the superiority of school-based vaccination and the feasibility of a broad catch-up campaign in the first year.

WEB: http://dx.doi.org/10.1016/j.vaccine.2015.05.078
IMPACT FACTOR: 3.49
CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: Bhutan was the first low/middle income country to introduce HPV vaccination into its routine immunization activities through a school-based program, and this article discusses challenges and successes of HPV vaccine delivery. School-based delivery, while preferable to health center delivery in terms of coverage, faced barriers in timing and the consent process. The authors conclude that it is important to consider the school calendar and seasonal weather patterns (e.g. monsoon) carefully when scheduling vaccination activities, and to tailor the consent process to protect those vaccinated but also to avoid stigma and suspicions about safety.
4. METHODS AND CHALLENGES IN MEASURING THE IMPACT OF NATIONAL PNEUMOCOCCAL AND ROTAVIRUS VACCINE INTRODUCTION ON MORBIDITY AND MORTALITY IN MALAWI.

Bar-Zeev N, Kapanda L, King C, Beard J, Phiri T, Mvula H et al.

PMID: 25917672

ABSTRACT

BACKGROUND: Pneumonia and gastroenteritis are leading causes of vaccine-preventable childhood morbidity and mortality. Malawi introduced pneumococcal conjugate and rotavirus vaccines to the immunisation programme in 2011 and 2012, respectively. Evaluating their effectiveness is vital to ensure optimal implementation and justify sustained investment.

METHODS/DESIGN: A national evaluation platform was established to determine vaccine effectiveness and impact in Malawi. Impact and effectiveness against vaccine-type invasive pneumococcal disease, radiological pneumonia and rotavirus gastroenteritis are investigated using before-after incidence comparisons and case-control designs, respectively. Mortality is assessed using a prospective population cohort. Cost-effectiveness evaluation is nested within the case-control studies. We describe platform characteristics including strengths and weaknesses for conducting vaccine evaluations.

DISCUSSION: Integrating data from individual level and ecological methods across multiple sites provides comprehensive information for policymakers on programme impact and vaccine effectiveness including changes in serotype/genotype distribution over time. Challenges to robust vaccine evaluation in real-world conditions include: vaccination ascertainment; pre-existing rapid decline in mortality and pneumococcal disease in the context of non-vaccine interventions; and the maintenance of completeness and quality of reporting at scale and over time. In observational non-randomised designs ascertainment of vaccine status may be biased particularly in infants with fatal outcomes. In the context of multiple population level interventions targeting study endpoints attribution of reduced incidence to vaccine impact may be flawed. Providing evidence from several independent but complementary studies will provide the greatest confidence in assigning impact. Welcome declines in disease incidence and in child mortality make accrual of required sample sizes difficult, necessitating large studies to detect the relatively small but potentially significant contribution of vaccines to mortality prevention. Careful evaluation of vaccine effectiveness and impact in such settings is critical to sustaining support for vaccine programmes. Our evaluation platform covers a large population with a high prevalence of HIV and malnutrition and its findings will be relevant to other settings in sub-Saharan Africa.

WEB: http://dx.doi.org/10.1016/j.vaccine.2015.04.053

IMPACT FACTOR: 3.49

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: Studies of vaccine effect on disease incidence and mortality, and vaccine cost-effectiveness were conducted using data from 3 sources: 1) a rural demographic surveillance population, 2) under-5 mortality surveillance in 2000 villages in central Malawi and 3) surveillance data from Blantyre on invasive pneumococcal disease. Figure 1 outlines the studies conducted at each site, while Table 4 describes challenges, potential impacts, and mitigation strategies in vaccine evaluation at scale.
5. PSYCHOSOCIAL DETERMINANTS OF CHINESE PARENTAL HPV VACCINATION INTENTION FOR ADOLESCENT GIRLS: PREVENTING CERVICAL CANCER.

Wang LD, Lam WW, Wu J, Fielding R.
Psychooncology. 2015 Jun 4. [Epub ahead of print]
PMID: 26042656

ABSTRACT

BACKGROUND: Intention is an important precursor of decisions to undergo vaccination. Using an extensively modified theory of planned behaviour, we explored psychosocial determinants of vaccination intention against human papillomavirus (HPV) among Hong Kong Chinese parents.

METHODS: A random sample of 368 (response rate 54.6%) Chinese parents who had at least one daughter aged 12-17 years, had heard of HPV vaccine before but had not vaccinated daughters against HPV and had completed telephone interviews between February and April 2014. Hierarchical multiple regression analysis examined the additive effect of theoretical constructs. Stepwise multiple regression analysis determined which variables contributed the most to the prediction of vaccination intention.

RESULTS: Principal determinants of parental HPV vaccination intention were anticipated worry if not vaccinated (β = 0.23, p = 0.001), anticipated anxiety reduction after HPV vaccination (β = 0.19, p = 0.005), proneness to peer influence (β = 0.17, p = 0.002), private health insurance for children (β = 0.14, p = 0.009), perceiving daughter's susceptibility to cervical cancer (β = 0.17, p = 0.003), number of daughters (β = -0.13, p = 0.011), descriptive norms of HPV vaccination (β = 0.13, p = 0.021), perceiving cervical cancer as behaviour-preventable disease (β = -0.11, p = 0.031) and anticipated regret if not vaccinated (β = 0.14, p = 0.046). Cervical cancer-related worry/anxiety explained 32.8% of the variance in parental HPV vaccination intention.

CONCLUSIONS: Results suggest that cervical cancer-related worry/anxiety is the most important predictor of parental HPV vaccination intention in Hong Kong Chinese and possibly other populations. Social influences also play an important role affecting parental vaccination intention, particularly peer influence and descriptive norm beliefs. Implications of these results are discussed in terms of future HPV vaccination promotion and cervical cancer prevention programme.

WEB: http://dx.doi.org/10.1002/pon.3859
IMPACT FACTOR: 4.04
CITED HALF-LIFE: 5.90

UW EDITORIAL COMMENT: The authors suggest several strategies based on their findings: Public health messaging to build upon parents' desires to adhere to social norms and prevention programs highlighting the generally high prevalence of HPV infection, to communicate that infection is not only associated with certain behaviors, such as sexual promiscuity. Drawbacks of this study include the low response rate, which limits the interpretability of these findings.
6. COMBINATIONS OF QUALITY AND FREQUENCY OF IMMUNIZATION ACTIVITIES TO STOP AND PREVENT POLIOVIRUS TRANSMISSION IN THE HIGH-RISK AREA OF NORTHWEST NIGERIA.

Duinjter Tebbens RJ, Pallansch MA, Wassilak SG, Cochi SL, Thompson KM.
PMID: 26068928

ABSTRACT

BACKGROUND: Frequent supplemental immunization activities (SIAs) with the oral poliovirus vaccine (OPV) represent the primary strategy to interrupt poliovirus transmission in the last endemic areas.

MATERIALS AND METHODS: Using a differential-equation based poliovirus transmission model tailored to high-risk areas in Nigeria, we perform one-way and multi-way sensitivity analyses to demonstrate the impact of different assumptions about routine immunization (RI) and the frequency and quality of SIAs on population immunity to transmission and persistence or emergence of circulating vaccine-derived polioviruses (cVDPVs) after OPV cessation.

RESULTS: More trivalent OPV use remains critical to avoid serotype 2 cVDPVs. RI schedules with or without inactivated polio vaccine (IPV) could significantly improve population immunity if coverage increases well above current levels in under-vaccinated subpopulations. Similarly, the impact of SIAs on overall population immunity and cVDPV risks depends on their ability to reach under-vaccinated groups (i.e., SIA quality). Lower SIA coverage in the under-vaccinated subpopulation results in a higher frequency of SIAs needed to maintain high enough population immunity to avoid cVDPVs after OPV cessation.

CONCLUSIONS: National immunization program managers in northwest Nigeria should recognize the benefits of increasing RI and SIA quality. Sufficiently improving RI coverage and improving SIA quality will reduce the frequency of SIAs required to stop and prevent future poliovirus transmission. Better information about the incremental costs to identify and reach under-vaccinated children would help determine the optimal balance between spending to increase SIA and RI quality and spending to increase SIA frequency.

WEB: http://dx.doi.org/10.1371/journal.pone.0130123

IMPACT FACTOR: 3.53

CITED HALF-LIFE: 2.40

UW EDITORIAL COMMENT: This modeling study evaluates several strategies to reduce persistence or re-emergence of vaccine-derived polioviruses (cVDPV) after OPV(2) cessation. They first focus on parameters that most effect population immunity to all 3 serotypes, and then focus on quality and frequency of tOPV SIAs.
7. MICRONEEDLE-BASED DRUG AND VACCINE DELIVERY VIA NANOPOROUS MICRONEEDLE ARRAYS.

Drug Deliv Transl Res. 2015 Jun 5. [Epub ahead of print].
PMID: 26044672

ABSTRACT

In the literature, several types of microneedles have been extensively described. However, porous microneedle arrays only received minimal attention. Hence, only little is known about drug delivery via these microneedles. However, porous microneedle arrays may have potential for future microneedle-based drug and vaccine delivery and could be a valuable addition to the other microneedle-based drug delivery approaches. To gain more insight into porous microneedle technologies, the scientific and patent literature is reviewed, and we focus on the possibilities and constraints of porous microneedle technologies for dermal drug delivery. Furthermore, we show preliminary data with commercially available porous microneedles and describe future directions in this field of research.

WEB: http://dx.doi.org/10.1007/s13346-015-0238-y

IMPACT FACTOR: 0.00
CITED HALF-LIFE: 0.00

UW EDITORIAL COMMENT: Figure 2 shows photos of two different nanoporous ceramic microneedle arrays—one with 16 microneedles at a length of 370 µm, and one with 126 microneedles and a length of 200 µm. Figure 4 shows the loading and release data for fluorescently labeled nanoparticles loaded into nanoporous ceramic microneedle arrays. More research will have implications for vaccine delivery in both high- and low-income settings.
8. SUBSTANTIAL DECLINE IN HEPATITIS B VIRUS INFECTIONS FOLLOWING VACCINE INTRODUCTION IN TAJIKISTAN.

PMID: 26072015

ABSTRACT

BACKGROUND: Tajikistan, considered highly endemic area for hepatitis B virus (HBV) in a pre-vaccine era, introduced hepatitis B vaccine in 2002 and reported ≥80% coverage with three doses of hepatitis B vaccine (HepB3) since 2004. However, the impact of vaccine introduction has not been assessed.

METHODS: We tested residual serum specimens from a 2010 national serosurvey for vaccine-preventable diseases in Tajikistan and assessed the prevalence of HBV infection across groups defined based on the birth cohorts' routine infant hepatitis B vaccination program implementation and HepB3 coverage achieved (≥80% versus <80%). Serosurvey participants were selected through stratified multi-stage cluster sampling among residents of all regions of Tajikistan aged 1-24 years. All specimens were tested for antibodies against HBV core antigen (anti-HBc) and those found positive were tested for HBV surface antigen (HBsAg). Seroprevalence and 95% confidence intervals were calculated and compared across subgroups using Satterthwaite-adjusted chi-square tests, accounting for the survey design and sampling weights.

RESULTS: A total of 2188 samples were tested. Prevalence of HBV infection markers was lowest among cohorts with ≥80% HepB3 coverage (ages, 1-6 years): 2.1% (95% confidence interval, 1.1-4.3%) for anti-HBc, 0.4% (0.1-1.3%) for HBsAg, followed by 7.2% (4.1-12.4%) for anti-HBc and 2.1% (0.7-6.1%) for HBsAg among cohorts with <80% HepB3 coverage (ages, 7-8 years), by 12.0% (8.7-16.3%) for anti-HBc and 3.5% (2.2-5.6%) for HBsAg among children's cohorts not targeted for vaccination (ages, 9-14 years), and 28.9% (24.5-33.8%) for anti-HBc and 6.8% (4.5-10.1%) for HBsAg among unvaccinated adult cohorts (ages, 15-24 years). Differences across groups were significant (p<0.001, chi-square) for both markers.

CONCLUSIONS: The present study demonstrates substantial impact of hepatitis B vaccine introduction on reducing HBV infections in Tajikistan. To achieve further progress in hepatitis B control, Tajikistan should maintain high routine coverage with hepatitis B vaccine, including birth dose.

WEB: http://dx.doi.org/10.1016/j.vaccine.2015.05.092

IMPACT FACTOR: 3.49

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: Table 4 shows the prevalence of antibody to hepatitis B virus core antigen (anti-HBc) and hepatitis B virus surface antigen (HBsAg) in the population-based serosurvey. Limitations of this study should be noted: the sample size of children older than five years in the cohort was small. In addition, the authors draw favorable conclusions based on small or seemingly selected comparison groups. For example, in Table 4, they report the results for children ages 1-6 where vaccination rates are >80% but the WHO definition stipulates a comparison of children >5 y/o.

PMID: 26010084

ABSTRACT

INTRODUCTION: India was the last country in the world to implement a two-dose strategy for measles-containing vaccine (MCV) in 2010. As part of measles second-dose introduction, phased measles vaccination campaigns were conducted during 2010-2013, targeting 131 million children 9 months to <10 years of age. We performed a post-campaign coverage survey to estimate measles vaccination coverage in Jharkhand state.

METHODS: A multi-stage cluster survey was conducted 2 months after the phase 2 measles campaign occurred in 19 of 24 districts of Jharkhand during November 2011-March 2012. Vaccination status of children 9 months to <10 years of age was documented based on vaccination card or mother's recall. Coverage estimates and 95% confidence intervals (95% CI) for 1,018 children were calculated using survey methods.

RESULTS: In the Jharkhand phase 2 campaign, MCV coverage among children aged 9 months to <10 years was 61.0% (95% CI: 54.4-67.7%). Significant differences in coverage were observed between rural (65.0%; 95% CI: 56.8-73.2%) and urban areas (45.6%; 95% CI: 37.3-53.9%). Campaign awareness among mothers was low (51.5%), and the most commonly reported reason for non-vaccination was being unaware of the campaign (69.4%). At the end of the campaign, 53.7% (95% CI: 46.5-60.9%) of children 12 months to <10 years of age received ≥2 MCV doses, while a large proportion of children remained under-vaccinated (34.0%, 95% CI: 28.0-40.0%) or unvaccinated (12.3%, 95% CI: 9.3-16.2%).

CONCLUSIONS: Implementation of the national measles campaign was a significant achievement towards measles elimination in India. In Jharkhand, campaign performance was below the target coverage of ≥90% set by the Government of India, and challenges in disseminating campaign messages were identified. Efforts towards increasing two-dose MCV coverage are needed to achieve the recently adopted measles elimination goal in India and the South-East Asia region.

WEB: http://dx.doi.org/10.1371/journal.pone.0127105
IMPACT FACTOR: 3.53
CITED HALF-LIFE: 2.40
UW EDITORIAL COMMENT: Table 4 shows reasons for non-vaccination and awareness of the vaccination campaigns in both urban and rural areas. Findings of this survey indicate that school staff and local health workers are the most effective disseminators of vaccination campaign information; mass media was far less effective.
10. OPPORTUNITIES TO IMPROVE POSTPARTUM CARE FOR MOTHERS AND INFANTS: DESIGN OF CONTEXT-SPECIFIC PACKAGES OF POSTPARTUM INTERVENTIONS IN RURAL DISTRICTS IN FOUR SUB-SAHARAN AFRICAN COUNTRIES.


PMID: 26038100

ABSTRACT

BACKGROUND: Postpartum maternal and infant mortality is high in sub-Saharan Africa and improving postpartum care as a strategy to enhance maternal and infant health has been neglected. We describe the design and selection of suitable, context-specific interventions that have the potential to improve postpartum care.

METHODS: The study is implemented in rural districts in Burkina Faso, Kenya, Malawi and Mozambique. We used the four steps ‘systems thinking’ approach to design and select interventions: 1) we conducted a stakeholder analysis to identify and convene stakeholders; 2) we organised stakeholders causal analysis workshops in which the local postpartum situation and challenges and possible interventions were discussed; 3) based on comprehensive needs assessment findings, inputs from the stakeholders and existing knowledge regarding good postpartum care, a list of potential interventions was designed, and; 4) the stakeholders selected and agreed upon final context-specific intervention packages to be implemented to improve postpartum care.

RESULTS: Needs assessment findings showed that in all study countries maternal, newborn and child health is a national priority but specific policies for postpartum care are weak and there is very little evidence of effective postpartum care implementation. In the study districts few women received postpartum care during the first week after childbirth (25 % in Burkina Faso, 33 % in Kenya, 41 % in Malawi, 40 % in Mozambique). Based on these findings the interventions selected by stakeholders mainly focused on increasing the availability and provision of postpartum services and improving the quality of postpartum care through strengthening postpartum services and care at facility and community level. This includes the introduction of postpartum home visits, strengthening postpartum outreach services, integration of postpartum services for the mother in child immunisation clinics, distribution of postpartum care guidelines among health workers and upgrading postpartum care knowledge and skills through training.

CONCLUSION: There are extensive gaps in availability and provision of postpartum care for mothers and infants. Acknowledging these gaps and involving relevant stakeholders are important to design and select sustainable, context-specific packages of interventions to improve postpartum care.

WEB: http://dx.doi.org/10.1186/s12884-015-0562-8

IMPACT FACTOR: 2.15

CITED HALF-LIFE: 3.40

UW EDITORIAL COMMENT: Needs assessment for improving post-partum care suggests that the high uptake of routine vaccination at health facilities suggests may make this be a good platform to integrate post-partum care.
APPENDIX: PUBMED SEARCH TERMS


*On June 22, 2015, this search of English language articles published between May 15, 2015 and June 14, 2015 and indexed by the US National Library of Medicine resulted in 182 unique manuscripts.