Council on Health Research for Development: COHRED Important research advancing global health

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Important discoveries past twenty years and present

A. Basic Science

A.1. Reverse Vaccinology. Even though it's been almost 20 years since the first complete genome sequence of an organism, the archaeon Methanococcus jannaschii was completed (1996), the field of genomics and genome sequencing has not yet yielded an abundance of new products, i.e., drugs, diagnostics, and vaccines for neglected diseases or global health. An important exception has been pioneered by Dr. Rino Rappuoli at Novartis Vaccines and Diagnostics who created the field of reverse vaccinology. Through high throughput in silico screening of an entire genome to identify genes that encode proteins with the attributes of a good vaccine, followed by moderate throughput expression and testing in laboratory mice model, the process of reverse vaccinology has been applied to several bacterial pathogens including group B Neisseria meningitidis, several Streptococcus species, and Escherichia coli. The first vaccine discovered through reverse vaccinology, the meningococcal B vaccine is now in phase 3 trials and could become one of the first licensed products discovered through OMICs approaches.

A lesson learned is the importance of having a champion such as Dr. Rappuoli to lead this approach as well as organizational commitment and willingness to apply cutting edge science to attacking global health problems.

Investing in the future: A big question is whether this approach could be applied to more complex parasitic organisms and how widely this approach can be used for other infectious pathogens.

Reference paper: Seib K, Zhao X, Rappuoli R. 2012. Developing vaccines in the era of genomics: a decade of reverse vaccinology. Clin Microbiol Infect Suppl 5: 109-16.

B. Product Development and Translational Medicine

B.1. MenAfriVac*: The Meningococcal A vaccine*. Through the activities of PATH Vaccines based in Washington DC and collaboration with the Serum Institute of India the Meningitis Vaccine Project was established in 2001 with funding from the Bill & Melinda Gates Foundation. The MenAfriVac received Indian market authorization in December of 2009 and WHO prequalification in June 2010 and introduced at public health scale in Burkina Faso, Mali, and Niger in Africa's meningitis belt in December 2010, and is now leading to the elimination of that disease.

A lesson learned is demonstrating how a global health product could be developed without the involvement of a major multinational pharmaceutical corporation and instead through the involvement of a PDP (product development partnership) together with a developing country manufacturer, in this case Serum Institute of India.

Investing in the future: Additional support for PDPs and developing country manufacturers.

Reference paper: Frasch CE, Preziosi MP, LaForce FM. 2012. Development of a group A meningococcal conjugate vaccine, MenAfricVac ™. Hum Vaccin Immunother 8: 715-24.

B.2. Systems Vaccinology. A potential although yet unproven approach to vaccines is the systems vaccinology strategy proposed by Rino Rappuoli. Among other things this approach proposes a dramatically streamlined approach to clinical trials in order to shorten the timeframe from initial safety studies to licensure. There is an urgent need to reduce both the cost and the time required for clinical trials if we are to see new global health vaccines introduced over the next decade.

Reference paper: Rappuoli R, Aderem A. 2011. A 2020 vision for vaccines against HIV, tuberculosis, and malaria. Nature 473: 463-9.

C. Implementation Science

C.1. SAFE Strategy for Trachoma. In the early 1990s it was demonstrated that a single oral dose of azithromycin was as effective as the previously recommended regimen of 6 weeks of daily topical application of tetracycline to treat ocular trachoma infection. This led to early support by the Edna McConnell Clark Foundation followed by the launching of the International Trachoma Initiative, a partnership with Pfizer. Today trachoma is being eliminated through this strategy, while additional evidence points to enormous collateral benefits of yearly azithromycin for yaws and other infections, in some cases with enormous mortality reductions.

Investing in the future: The collateral impact of once yearly Zithromax has had important benefits on reducing yaws and also global mortality where it has been studied. Why? Is it through reductions in pneumococcal carriage? Diarrheal disease?

References

Bailey RL, Arullendran P, Whittle HC, Mabey DC. 1993. Randomised controlled trial of single-dose azithromycin in treatment of trachoma. Lancet 342: 453-6

Emerson PM, Burton M, Solomon A, Bailey R, Mabey D. 2006. The SAFE strategy for trachoma control: using operational research for policy, planning, and implementation. Bull WHO 84: 613-9.

Porco TC, Gebre T, Ayele B, House J, et al. 2009. Effect of mass distribution of azithromycin for trachoma control on overall mortality in Ethiopian children: a randomized trial. JAMA 302: 962-8.

Mabey D. 2012. Oral azithromycin treatment for yaws. Lancet 379: 295-7.

C.2. Integrating NTDs. In 2005, together with Profs. David Molyneux and Alan Fenwick in the UK, and Lorenzo Savioli at WHO and others, the concept of bundling together multiple chronic parasitic and related infections, which we termed the neglected tropical diseases (NTDs) was proposed, followed by targeting them simultaneously with a package of low cost and donated drugs. So far, this "rapid impact package" has been deployed to more than 250 million people

in low- and middle-income countries through support from USAID and DFID, as well as private support from an END (End Neglected Disease) fund.

A lesson learned is the recognition of the importance of co-infections that individual diseases do not occur in isolation and there is an opportunity to bundle interventions in resource-poor countries.

A second lesson learned is the importances of having the scientists themselves conduct public advocacy and policy.

A third lesson learned is the increasing recogntion that NTDs behave more like NCDs than infections and that NTDs account for an important yet stealth amount of NCD disease burden in developing countries.

Investing in the future: The importance of teasing out how much of the NCD global disease burden, including that resulting from cancer, renal and liver disease, as well as cardiovascular disease is actually from NTDs

Reference papers:

Molyneux DH, Hotez PJ, Fenwick A. 2005. "Rapid impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. PLOS Med 2: e336.

Hotez PJ, Molyneux DH, Fewnick A, et al. 2007. Control of neglected tropical diseases. N Engl J Med 357: 101827.

Hotez PJ, Daar A. 2008. The CNCDs and the NTDs: blurring the lines dividing the noncommunicable and communicable chronic diseases. PLOS Negl Trop Dis 2: e312.

C.3. Linking NTDs with HIV/AIDS and Malaria. Despite the observation that NTDs geographically overlap with HIV/AIDS and malaria in many developing countries and new evidence that female genital schistosomiasis increases the risk of acquiring HIV/AIDS by 3-4 fold while hookworm exacerbates malaria anemia, the major global programs for HIV/AIDS and

malaria are still separated from NTD control. There are additional operational benefits including the observation that anti malaria bednet distribution increases almost 9 fold when conducted through community drug distribution for NTDs.

A lesson learned is the barriers that are in place between major global public health programs despite the scientific evidence base for breaking them down.

Investing in the future: Support for operational research around the bundling or linking of these programs.

References

Hotez PJ, Molyneux DH, Fenwick A, et al. 2006. Incorporating a rapid impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis and malaria. PLOS Med 3: e102.

Hotez PJ, Mistry N, Rubinstein J, Sachs JD. 2011. Integrating neglected tropical diseases into AIDS, tuberculosis, and malaria control. N Engl J Med 364: 2086-9.

C.4. Community Led Total Sanitation. India's Kamal Kar has pioneered the concept of community led total sanitation for resource poor settings. His work is demonstrating how even with modest resources and without economic development, great strides can be made in a community as part of health systems strengthening. There is a need to apply operational research and implementation science to this activity.

Reference: http://www.communityledtotalsanitation.org/page/kamal-kar

C.5. A low-cost "poly-pill" for human cardiovascular disease. The opportunity for a low-cost statin combined with aspirin and a medicine to lower blood pressure has gained great interest as an approach to reducing the burden of non-communicable diseases in resource poor settings. Operational research around this concept is of enormous importance and interest.

Reference: Lonn E, Bosch J, Teo KK, et al. 2010. The polypill in the prevention of cardiovascular diseases. Circulation 122: 2078-2088.