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VACCINATION: ACHIEVEMENTS, CHALLENGES, PROSPECTS

CONTENT

VACCINATION: ACHIEVEMENTS, CHALLENGES, PROSPECTS

The history of vaccination is rich and full of success stories. It all started in 1768 when an English physician realised that prior infection with cowpox rendered a person immune to smallpox. After several investigations and tests in human beings in the years that followed, it was Edward Jenner, another physician in England, who observed that milkmaids were generally immune to smallpox. He postulated that pus in the blisters that milkmaids developed from cowpox (a disease similar to smallpox, but much less virulent) protected them from smallpox. In 1796, Jenner tested his hypothesis by inoculating an eight-year-old boy: he scraped pus from cowpox blisters on the hands of a milkmaid who had caught cowpox from a cow and inoculated the boy in both arms that same day. The boy developed a fever and some uneasiness, but no full-blown infection. The success of Jenner's discovery soon spread around Europe, with small pox vaccination also being used for traders in their expeditions to the Americas and the Far East. In 1980, following an historic global campaign of surveillance and vaccination, the World Health Assembly declared smallpox eradicated – the only infectious disease so far to achieve this distinction.

Polio (poliomyelitis) is another contagious disease that could be eradicated, as there is an effective and inexpensive vaccine providing life-long immunity. The Polio Eradication Initiative is a UN programme with the target of a polio-free world. Initially experts believed this could be achieved by the year 2005, but that proved unrealistic. For a region or continent to be certified as polio-free, there must be no detection of wild poliovirus for three consecutive years as well as an appropriate surveillance system. Recently, polio got one step closer to becoming the second human disease to be fully wiped out. On 24 October 2019, World Polio Day, the World Health Organization announced that type 3 poliovirus has been eradicated worldwide. For polio to be fully eradicated, all three wild polio strains (types 1, 2 and 3) need to stop circulating. The three strains all cause the same horrible symptoms, including paralysis and death, but are virologically distinct. Type 2 was eradicated back in 2015; the last case of type 3 polio surfaced in northern Nigeria in 2012 and the virus hasn't been seen since. Today, only type 1 remains at large — in Afghanistan and Pakistan. Enormous efforts are being made to finally eradicate polio completely.

Many other diseases are being prevented through routine vaccination programmes or through mass vaccination in the event of outbreaks. But there is a whole series of conditions that determine the success of such efforts. In this edition of MT*b*, you can read about vaccination surveillance in the Netherlands by our National Institute of Health and the Environment (RIVM) – illustrated by the example of maternal pertussis (whooping cough) which was added to the Dutch national immunisation programme in December 2019. The media recently paid a lot of attention to reluctance among the general public in the Netherlands towards vaccination, showing that high coverage rates are not to be taken for granted. Two articles in this edition reflect on what it takes to safeguard high vaccination rates.

Two other articles provide insight into global mechanisms to ensure sustainable financing of vaccination programmes (the case of GAVI) and reliable vaccine provision (the case of ICG). The recent approval of an Ebola vaccine (November 2019) made news headlines and several authors refer to it. If you are interested in the latest on vaccine development for TB and malaria, we recommend the first two articles of this edition. Enjoy the reading!

Leon Bijlmakers, Jan Auke Dijkstra

New developments in TB vaccine and correlate research offer real hope for better TB vaccines

Tuberculosis (TB) continues to pose an enormous threat to global health, with over one quarter of the world's population latently infected, over 10 million new active TB cases each year, over 1.3 million annual deaths, and an ever-rising frequency of multi-resistant Mtb strains.[1] Classical intradermal *M.bovis* Bacillus Calmette-Guerin (BCG) vaccination of neonates and young infants protects against severe forms of acute and early TB disease, with over 80% protective efficacy against TB meningitis, which can be rapidly fatal. Unfortunately, however, BCG vaccination fails to protect consistently and sufficiently against pulmonary TB in adults, which is the main form of contagious TB.[2] The reasons for this deficiency are not fully understood but may involve waning of memory, interference by other infections such as Non Tuberculous Mycobacterial (NTM) or certain viral infections (CMV, EBV) which can modulate immune responses. As a result BCG vaccination has relatively little impact on global TB transmission patterns, which is a reason for TB vaccine researchers and developers to promote TB vaccines that target adolescent TB.

DEVELOPING NEW TB VACCINES

Better TB vaccines could have significant impact against TB, and pre- and post-exposure vaccination with improved vaccines represents a cornerstone of the WHO End TB strategy which aims to end TB by 2035.[1] To discover and develop better TB vaccines, research efforts were initiated in the mid-1990s, sponsored both by private and public funding, particularly the European Commission.[3] Discovery and evaluation of new candidate TB vaccines initially focused on the preclinical and early clinical space, from which emerged a first candidate, namely MVA85A. This vaccine was based on a single *Mycobacterium tuberculosis* (Mtb) protein, called Ag85A, which was expressed in a non-replicating viral vector (MVA) and had been designed as a booster vaccine for individuals that already have been given BCG. Although the vaccine was immunogenic and protective in certain animal models of TB, it was unable to provide any additional protective efficacy against TB when administered as a booster vaccine following BCG, in a large phase 2b study in infants.[4] This disappointing result, which could have been due to the fact that the Ag85A antigen is insufficiently expressed by Mtb bacteria in the lung,[5] spurred additional efforts to develop better vaccines.

USING DIVERSE APPROACHES ENHANCES CHANCE OF SUCCESS

Five approaches have been actively pursued in the last decade:[3]

1. **Subunit vaccines** which are based on specific immunogenic components of the bacillus, such

Figure 1: Global Clinical Development of TB vaccines. (Reproduced from TBVI, see: https://www.tbvi.eu/what-we-do/pipeline-of-vaccines/)

as proteins, fusion proteins and lipids, which are typically admixed with innate immunity stimulating adjuvants;

2. **Virally vectored subunit vaccines** in which the subunit component is typically expressed from a genetic insert encoding a selected Mtb antigen (such as was the case for MVA85A);

3. **Improving BCG**, by inserting additional antigens or by genetic manipulation of the BCG genome to improve its immunogenicity;

4. **Attenuating Mtb** by deleting essential virulence genes, thus producing a safe and antigenically fully competent Mtb-like vaccine;

5. **Alternative delivery routes** using existing vaccines, such as BCG, for example via the mucosal route (the lung) assuming that the natural route of infection is the most relevant route of vaccine delivery, inducing local immunity and immune (resident) memory.

RECENT SUCCESSES IN TB VACCINE DEVELOPMENT

Candidate vaccines from all five categories are being evaluated for safety and immunogenicity in clinical phase 1/2 studies, and some already have been or are being evaluated in phase 2B/3 studies for vaccine efficacy (VE) using prevention of disease (PoD) or prevention of infection (PoI) as primary endpoints (Figure 1).

Recently the results from two large studies were reported, with highly encouraging outcomes, strongly suggesting that better TB vaccines indeed are possible. The most important results came from a study in which a subunit vaccine (category 1 above), called M72 (a fusion protein consisting of 2 immunogenic Mtb antigens), was given together with a strong adjuvant, called AS01E, to adults who were already latently (that is asymptomatically) infected with Mtb.[6] Most Mtb infected people who will develop TB in their lifetime will do so in the first two years after infection. The final 3-year follow-up report was recently reported. Encouragingly, the vaccine arm showed a 50% vaccine efficacy against developing TB, although a relatively limited number of cases was present in the control arm of this large phase 2B trial. Nevertheless, M72 has significant PoD VE, in the absence of major adverse effects.

This encouraging result needs follow up for longer periods of time in order to determine the longevity of the response, and to assess whether further boosting would be required to maintain or augment the VE. At this stage, the mechanism of action of M72+AS01E is unknown. It could involve innate immune driven responses, including trained innate immune memory of myeloid cells, and/or adaptive immune responses (clear CD4+ T cell responses were induced by M72) or both.[3,7] Understanding the immune mechanisms behind the protective effect will be important in order to systematically improve and further develop this or other similar vaccines. Besides determining the longevity of the protective effect, another relevant question is whether M72 also works well in non-Mtb infected persons, including in BCG vaccinated individuals. Notwithstanding these questions, this landmark M72 trial result represents the first promising signal for any new TB vaccine since a century, and now needs to be evaluated in large phase 3 trials in both infected and uninfected people.

A second promising result came from a BCG revaccination study.[8] In this complex study design both a subunit (H4/IC31) and a BCG revaccination arm were included in a setting in which (sustained) PoI rather than PoD was assessed. Infection was defined as having developed a positive immune test (IGRA test) against Mtb specific antigens. The most important result, which had not been anticipated, was that although neither vaccine protected against infection (i.e. IGRA conversion from negative to positive) only BCG revaccination protected significantly against sustained Mtb infection: in the BCG revaccination arm fewer persons had remained IGRA positive after 24 months, representing a 45% VE signal. This finding could suggest that the immune system is able to eradicate an already established infection from the human body once properly activated, in this case by revaccination. This interesting and important concept needs to be examined further, including novel animal models, as it could focus research efforts on Mtb eradication by vaccination.

UNDERSTANDING THE IMMUNE MECHANISMS BEHIND THE PROTECTIVE EFFECT

NEW CLINICAL AND PROMISING LATE PRECLINICAL APPROACHES

There are, as already outlined in Figure 1, several candidate vaccines in early stage clinical development. This includes live vaccines such as recombinant BCG and attenuated MTBVAC, other subunit vaccines such as H56, and aerosol based delivery of BCG into the human lung.[7] In parallel, advanced preclinical evaluation models (usually in non-human primates (NHP)) are being used to assess and compare additional TB vaccine delivery routes and systems. Some promising ones include: aerosol / pulmonary delivery of BCG in NHP, with excellent VE results;[9] intravenous delivery of BCG (with strong VE results; Seder et al, unpublished), and Rhesus monkey-CMV vectored multi-antigen subunit vaccines that are being tested in NHP models, again with striking VE effects.[10] In addition, combinatorial vaccines with heterologous prime/boost-regimens can likely be harnessed to further optimize protective immunity induced by vaccination.

THE IMPORTANCE OF TB CORRELATES OF PROTECTION

'Correlates', often referred to as 'biomarkers', are markers that correlate with important biological or medical

outcomes, for example disease or protection. Unfortunately, there are virtually no human correlates of protection against TB. This is a major bottleneck delaying TB vaccine evaluation and prioritisation, because such correlates could help to identify protective antigens, develop improved vaccines, and allow the demonstration of immunogenicity and potential VE at an early stage. Correlates would thus facilitate the selection and prioritisation of candidate TB vaccines for human clinical efficacy testing, and help reduce the protracted time scale, large size, and expense of human efficacy trials, thus significantly facilitating TB vaccine development. In addition, correlates could help guide preclinical animal studies and thus help minimize use of animals. Samples from well-defined human cohorts with various Mtb exposure or infection states, including long-term resisters (either resisting natural infection induced IGRA conversion or resisting TB progression once infected), samples from future controlled human mycobacterial challenge models, and – particularly important – from individuals from trials with TB vaccines demonstrating protective VE will be essential for accelerating correlate discovery, testing and validation.

In addition, correlates of risk for progressing from asymptomatic (latent) infection towards TB disease would be extremely useful, e.g. in stratifying individuals in observational and clinical intervention studies, including (therapeutic) vaccination and drug studies. Several first signatures were reported a few years ago [11-13], and some of these are currently being further refined (e.g. [14,15]).

Although beyond the scope of this short review, it is clear that correlate discovery and evaluation is a second major priority in the field of TB vaccine development.

CONCLUDING FUTURE OUTLOOK

In very recent years, TB vaccine research and TB correlate discovery have witnessed significant breakthroughs. This provides real hope for effective, life-saving TB vaccines, which are much needed to control the TB endemic, including multi-drug-resistant and extensively drug resistant TB, and to help reach the End TB goal by 2035.[1]

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REFERENCES

1. WHO. Global Tuberculosis Report. 2019.
2. Ottenhoff TH, Kaufmann SH. Vaccines against tuberculosis: where are we and where do we need to go? PLoS pathogens. 2012;8(5):e1002607.
3. Kaufmann SHE, Dockrell HM, Drager N et al. TBVAC2020: Advancing Tuberculosis Vaccines from Discovery to Clinical Development. Frontiers in immunology. 2017;8:1203.
4. Tameris MD, Hatherill M, Landry BS et al. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. Lancet 2013;381(9871):1021-8.
5. Coppola M, van Meijgaarden KE, Franken KL et al. New Genome-Wide Algorithm Identifies Novel In-Vivo Expressed Mycobacterium Tuberculosis Antigens Inducing Human T-Cell Responses with Classical and Unconventional Cytokine Profiles. Scientific reports. 2016;6:37793.
6. Tait DR, Hatherill M, Van Der Meeren O et al. Final analysis of a trial of M72/AS01E vaccine to prevent Tuberculosis. New England J Med, 29th October 2019.
7. Andersen P, Scriba TJ. Moving tuberculosis vaccines from theory to practice. Nature Reviews Immunology. 2019;19(9):550-62.
8. Nemes E, Geldenhuys H, Rozot V et al. Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination. The New England journal of medicine. 2018;379(2):138-49.
9. Dijkman K, Sombroek CC, Vervenne RAW et al. Prevention of tuberculosis infection and disease by local BCG in repeatedly exposed rhesus macaques. Nature Medicine. 2019;25(2):255-62.
10. Hansen SG, Zak DE, Xu G et al. Prevention of tuberculosis in rhesus macaques by a cytomegalovirus-based vaccine. Nature Medicine. 2018;24(2):130-43.
11. Zak DE, Penn-Nicholson A, Scriba TJ et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet 2016;387(10035):2312-22.
12. Fletcher HA, Snowden MA, Landry B et al. T-cell activation is an immune correlate of risk in BCG vaccinated infants. Nature Communications. 2016;7:11290.
13. Sloot R, Schim van der Loeff MF, van Zwet EW et al. Biomarkers can identify pulmonary Tuberculosis in HIV-infected drug users months prior to clinical diagnosis. EBioMedicine. 2015;2(2):172-9.
14. Suliman S, Luabeya AKK, Geldenhuys H et al. Dose Optimization of H56:IC31 Vaccine for Tuberculosis-endemic populations. A double-blind, placebo-controlled, dose-selection trial. American J Respirat Critical Care Medicine. 2019;199(2):220-31.
15. Penn-Nicholson A, Hraha T, Thompson EG et al. Correction: Discovery and validation of a prognostic proteomic signature for tuberculosis progression: A prospective cohort study. PLoS Medicine. 2019;16(7):e1002880.

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Malaria vaccine development: silver bullet or shot in the dark?

Despite encouraging reductions in the global burden of malaria in the early 21st century, progress has since stagnated, particularly in the most heavily affected areas of sub-Saharan Africa. Implementation of an effective malaria vaccine is considered essential to bolster existing tools (e.g., effective case management, intermittent presumptive treatment, seasonal malaria chemoprevention, and vector management) and underpin control, or even perhaps for eradication of malaria. Ideally, a malaria vaccine would be integrated into the World Health Organization's (WHO) Expanded Programme of Immunisation, benefitting from the programme's existing management and logistics in order to effectively target those at greatest risk for malaria, i.e. infants and children.

So where are we currently in terms of malaria vaccine development – do we have a silver bullet in hand, or is it still just a 'shot' (of vaccine) in the dark? After presenting some background, we will discuss the current developmental status and prospects of three promising examples of vaccines that target *Plasmodium falciparum*, the most severe strain of malaria parasites globally.

RTS,S AS01 (MOSQUIRIX™)

Development of RTS,S started in the late 1980s, following the discovery that immune responses against *P. Falciparum* Circumsporozoite Protein (CSP) play an important role in protection against infection. CSP is the most abundant protein on the surface of sporozoites, the infectious form of the parasite transmitted by mosquitoes to people. The RTS,S vaccine consists of recombinant (synthetically produced) sections of CSP, fused and combined with recombinant hepatitis B surface antigen (HBsAg). The addition of HBsAg helps to strengthen the immune response against CSP, but also induces potent immunity against hepatitis B virus. RTS,S is administered in a strong adjuvant, AS01, to further boost immune responses.

Figure 1 summarises the developmental history of RTS,S, illustrating just how long such processes can take. Initial clinical testing was conducted in trials in malaria-naïve U.S. adult volunteers in the mid-90s, demonstrating safety and protection against Controlled Human Malaria Infections (CHMI). Such studies, in which subjects are deliberately infected with laboratory-cultured malaria parasites under highly controlled conditions, have proven themselves an invaluable tool for advancing the clinical development of promising vaccine candidates. The first trials of RTS,S in African (Gambian) adults were conducted around the millennium, but efficacy against naturally-acquired infection proved somewhat disappointing, protecting against only about 34% of infections. Despite this setback, over the next decade further testing was conducted in children and finally in infants, initially in Mozambique and subsequently in pivotal phase-3 trials in several counties across sub-Saharan Africa. RTS,S has consistently demonstrated a good safety and tolerability profile, but at ~18-36% protection against episodes of clinical malaria, efficacy remains well below the target threshold of 75% set by the WHO.[1,2] Protection against severe malaria is lower still (1% to 32%). A partial explanation for this relatively disappointing efficacy against naturally-acquired malaria infection may be that the vaccine only protects well against circulating *P. falciparum* strains that genetically resemble the vaccine.[3] Moreover, protection is of relatively short duration, waning within 3 years of initial immunisation. Indeed, it has been suggested that RTS,S may even cause a rebound-effect, whereby susceptibility to malaria is increased in the long term compared to unvaccinated subjects, at least in high-transmission areas, due to slower induction of naturally-acquired immunity in vaccinees.[4] In an attempt to overcome waning

Figure 1: Developmental history of RTS,S AS01 (Mosquirix™) vaccine.
EMA – European Medicines Agency; GSK – GlaxoSmithKline; WRAIR – Walter Reed Army Institute of Research.

immunity, a subset of participants in the phase 3 trials were administered a booster dose at 20 months after initial immunisation; over 3-4 years of follow-up, protection was indeed poorer in subjects who did not receive a booster. Importantly, protection is also relatively poorer in areas of high transmission, and in infants as compared to children.[2]

Based on these results, in 2015 (some 30 years since its first development) RTS,S nevertheless received regulatory approval from the European Medicines Agency – the first malaria vaccine ever to do so. Before taking a decision on whether to recommend the widescale implementation of RTS,S, however, WHO has requested further large-scale post-licensure trials. These commenced earlier this year in Ghana, Kenya and Malawi and will last until 2024. Some issues that remain to be resolved in these trials are whether it is feasible logistically to target vaccine recipients for a booster dose, and whether the marginally increased (but still extremely low) risk of cerebral malaria and meningitis in children and a slight increase in all-cause mortality in girls as observed in RTS,S recipients in the phase 3 studies represent genuine associations or merely chance post-hoc findings.[5]

ATTENUATED WHOLE SPOROZOITE-BASED VACCINES

In an attempt to improve upon the protection induced by RTS,S, other researchers have been developing second-generation vaccines consisting of attenuated live sporozoites. Live-attenuated vaccines are widely used against other diseases (e.g., measles, yellow fever and BCG for TBC) , are believed to induce stronger, broader and longer-lasting immune responses, and were first pioneered for malaria by Ruth and Victor Nussenzweig in the 1960s and '70s.[6] Sporozoites can be attenuated by radiation, genetic modification, or concomitant administration of chemoprophylaxis. The objective in all cases is to ensure that these inoculated sporozoites abort their development before themselves becoming pathogenic blood-stage parasites; in the process they are exposed to the immune system, inducing protective immune responses against subsequent infections (Figure 2).

In a landmark study, researchers at Radboud UMC (Nijmegen) pioneered a highly efficacious form of immunisation known as ChemoProphylaxis-with-Sporozoites (CPS), whereby subjects are inoculated with infectious sporozoites by mosquito bites whilst taking anti-malarial prophylaxis (usually chloroquine or mefloquine) to kill any parasites emerging from the liver into the blood-stream.[7] Alongside colleagues from Leiden UMC and Erasmus MC (Rotterdam), they have advanced this concept in a series of successful CHMI studies. This immunisation strategy, although not practically implementable on a large scale in resource-poor settings, remains the most potent known method for inducing immunity against malaria.[8]

The success of CPS has led to resurgent interest in the potential of attenuated whole-sporozoite vaccines. An important player in this field has been the U.S. biotech start-up Sanaria Inc., which pioneered a method to purify live aseptic *P. falciparum* sporozoites (PfSPZ) from the salivary glands of laboratory-reared mosquitoes and cryopreserve these in vials stored in liquid nitrogen. These can be shipped all over the world, thawed and administered intravenously by needle & syringe. This has helped to accelerate global vaccine development by allowing clinical trials to be conducted where they are most relevant, in resource-poor settings in sub-Saharan Africa. Indeed, Sanaria's PfSPZ Vaccine, consisting of radiation-attenuated sporozoites, has over

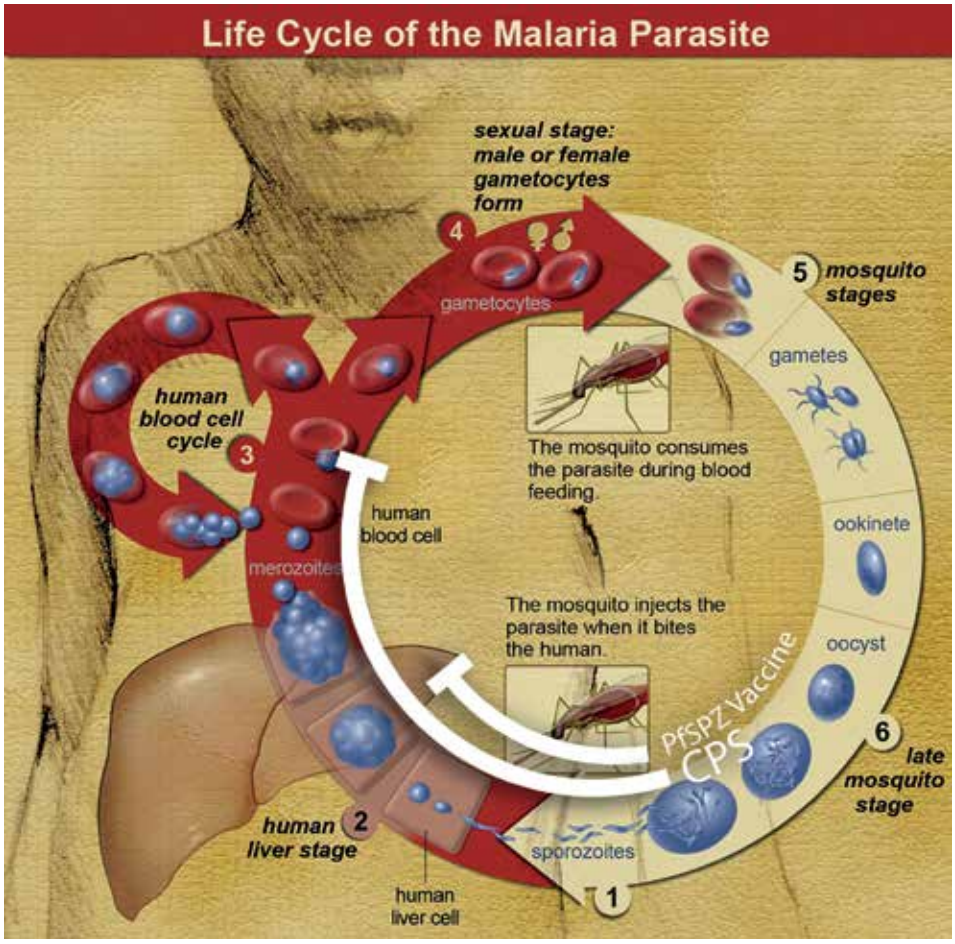

Figure 2: Life cycle of malaria parasites. Attenuated live sporozoites (white semicircles) abort their development before becoming pathogenic blood-stage parasites, in the process allowing the host to develop protective immune responses against subsequent infections. Irradiated sporozoites (e.g., PfSPZ Vaccine) arrest early during liver-stage development. In ChemoProphylaxis-with-Sporozoites (CPS), sporozoites complete liver-stage development but fail to multiply within red blood cells due to concomitant chemoprophylaxis. (Modified from Wikimedia Commons. Original source: National Institutes of Health.)

the past decade undergone testing in African adults, children and infants in amongst others Tanzania, Kenya, Mali, Gabon and Equatorial Guinee.[9]

Reminiscent of RTS,S however, protection in African populations, particularly infants, appears to be somewhat poorer than in malaria-naïve adult volunteers exposed to CHMI in Europe and the U.S. Potential explanations, including immaturity of young children's immune systems, immunosuppressive effects of prior malaria exposure and/or helminth co-infections, and parasite strain diversity, remain to be elucidated. Despite these set-backs, PfSPZ Vaccine is set to undergo large-scale testing in a phase 3 trial in Equatorial Guinee later this year.

TRANSMISSION-BLOCKING VACCINES

Vaccines targeting gametocytes (the parasite forms taken up by mosquitoes to complete malaria's life cycle) can help to reduce transmission. Although such a vaccine would not directly benefit its recipient, it could reduce cases of malaria in the community and indirectly even the recipient's own chances of re-infection. Such an altruistic vaccine could conceivably be added to a multi-component vaccine that also induces direct protection against infection or disease.

Several candidate vaccines induce potent transmission-blocking immunity in animal models and are currently undergoing clinical development. A leading example is Pfs48/45, a gametocyte protein shown by researchers at Radboud UMC to form a critical link in mosquito-transmission. A recombinant vaccine, R0.6C, based on this protein is set to undergo testing here in first-in-human clinical trials in 2020, including assessment of transmission-blocking activity.[10]

PERSPECTIVES

After years of largely unsuccessful attempts, exciting progress is now also being made towards a blood-stage malaria vaccine, based on reticulocyte-binding protein homolog 5 (RH5) that plays an essential role in the invasion of erythrocytes by P. falciparum merozoites. A first phase 1 trial of this vaccine induced antibodies with potent ability to inhibit invasion.[11]

In parallel with the clinical development of these vaccine strategies, state-of-the-art technologies such as genetically-attenuated parasite strains and passive immunisation with recombinant monoclonal antibodies are making inroads in the *P. falciparum* vaccine field, with significant contributions from researchers in the Netherlands, and offer great promise for the future. Moreover, vaccines against the world's second most dangerous malaria parasite, P. vivax, are also starting to be developed.

Malaria vaccine development's slow track record, and particularly the relatively disappointing efficacy of candidate vaccines in naturally-exposed populations, should of course caution against hubris. In parallel with empirical vaccine development, the field needs to develop a better understanding of fundamental obstacles to malaria immunity, including strain-diversity – currently a major area of research focus at amongst others Radboud UMC. That said, rational approaches and dedicated effort have already advanced malaria vaccine development well beyond a proverbial shot in the dark. Several shiny-looking bullets look set to be added to our anti-malarial arsenal and with concerted research one will yet be crafted of true 'silver'.

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REFERENCES

1. Rts S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015;386(9988):31-45.
2. Moorthy VS, Newman RD, Okwo-Bele J-M. Malaria vaccine technology roadmap. Lancet. 2013;382(9906):1700-1.
3. Neafsey DE, Juraska M, Bedford T et al. Genetic diversity and protective efficacy of the RTS,S/AS01 malaria vaccine. N Engl J Med. 2015;373(21):2025-37.
4. Olotu A, Fegan G, Wambua J et al. Seven-Year Efficacy of RTS,S/AS01 malaria vaccine among young African children. N Engl J Med. 2016;374(26):2519-29.
5. Guerra Mendoza Y, Garric E et al. Safety profile of the RTS,S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa. Hum Vaccin Immunother. 2019;15(10):2386-98.
6. Nussenzweig RS, Vanderberg J, Most H et al. Protective immunity produced by the injection of x-irradiated sporozoites of plasmodium berghei. Nature. 1967;216(5111):160-2.
7. Roestenberg M, McCall M, Hopman J et al. Protection against a malaria challenge by sporozoite inoculation. N Engl J Med. 2009;361(5):468-77.
8. Sauerwein RW, Bijker EM, Richie TL. Empowering malaria vaccination by drug administration. Curr Opin Immunol. 2010;22(3):367-73.
9. Richie TL, Billingsley PF, Sim BKL et al. Progress with Plasmodium falciparum sporozoite (PfSPZ)-based malaria vaccines. Vaccine. 2015;33(52):7452-61.
10. Singh SK, Roeffen W, Andersen G et al. A Plasmodium falciparum 48/45 single epitope R0.6C subunit protein elicits high levels of transmission blocking antibodies. Vaccine. 2015;33(16):1981-6.
11. Payne RO, Silk SE, Elias SC et al. Human vaccination against RH5 induces neutralizing antimalarial antibodies that inhibit RH5 invasion complex interactions. JCI Insight. 2017;2(21).

WHO-INT

Overcoming the challenges in achieving high immunization coverage in low-income countries: the role of Gavi

When Ebola hit West Africa for the first time just five years ago, it was a little known, but much feared lethal disease. With no cure or vaccine available it could kill over 50% of people infected.[1] This, and the fact that people were unfamiliar with the disease and the way it spread, is why the disease was able to sweep across the region infecting more than 28,600 people and killing 11,300 of them. Upon the recommendation of the European Medicines Agency's scientific committee to recommend the approval of conditional market authorization for the world's first Ebola vaccine (in October 2019), which has been successfully deployed as an investigational product to fight the now waning outbreak in the Democratic Republic of the Congo, the World Health Organization formally announced its prequalification in mid-November. In less than half a decade, Ebola has gone from being nearly a death sentence to a vaccine-preventable disease.

The significance of this is two-fold. Firstly, national regulatory bodies can now choose to expedite their own approval for the vaccine, just five years after the West Africa outbreak, whereas the whole process can normally take well over a decade. And secondly, it is a vaccine against a disease that predominantly impacts some of the poorest communities in the world: the type of vaccine that would not traditionally attract major investment from pharmaceutical companies.

Its ability to clear these two hurdles is in part due to the work of Gavi, the Vaccine Alliance based in Geneva, which seeks to increase access to new and underused vaccines in low-income countries. At the end of the West African outbreak, Gavi sent a signal to the market that it would be there to purchase vaccines by committing to make up to USD 345 million available for Ebola vaccines. Then this particular vaccine was made available through an Advance Purchase Commitment agreement signed between Gavi and the vaccine manufacturer, Merck, in 2016. Gavi offered a USD 5 million pre-paid commitment to Merck in exchange for doses of the vaccine once it was licensed, under the condition that Merck would make a stockpile of investigational doses available for outbreak response as well as some regulatory requirements. It is these doses that have helped protect over 254,000 people against Ebola in DRC.[2]

This type of novel approach is indicative of the unique way that Gavi takes on the challenges that exist in increasing access to vaccines. Since 2000, the Vaccine Alliance has been helping protect some of the world's most vulnerable children against deadly and debilitating diseases by leveraging innovative partnerships, technologies, and financing mechanisms.

GAVI'S INCEPTION

In the late 1990s, new and underused vaccines were not reaching those people most in need of them because new vaccines were made in low volume for high priced markets and therefore, most vaccines were simply not available at prices that their countries could afford. For example, in 2000, hepatitis B infections were killing more than 900,000 people a year, the majority in developing countries. But even though a highly effective vaccine had been available in wealthy countries since 1982, only a minority of low-income countries had so far introduced it. At the same time, global coverage of routine immunization was also plateauing, with more than 30 million children in the world's poorest countries not being fully immunized even with the basic vaccines. Gavi's strategy was to bring together key players at the global and local level – country governments, UN agencies, and civil society organizations – to address the major mismatch between the people who had access to vaccines and the people who could benefit from them the most. By harnessing the financial resources and expertise of these different partners, Gavi aimed to increase the affordability and accessibility of life-saving vaccines.

SUSTAINABILITY GOAL

The most important partners within this Alliance are the implementing countries themselves. A cornerstone of the Gavi approach is that the organization works together with governments to build systems that they can sustainably finance well into the future, independently of Gavi support. The Gavi model requires all countries, no matter how poor, to contribute some proportion of the cost of the vaccines that they introduce through Gavi. As a country's economy grows, as measured by their gross national income per capita, so too does the proportion that they pay, until it reaches a point of transition where the government has five years to fully fund its vaccine programmes. So far, 15 countries have transitioned out of Gavi support, with three more expected by the end of 2020.

THE MARKET SHAPING GOAL

Addressing the affordability side involves leveraging predictability of demand and economies of scale to secure lower vaccine prices. Gavi

purchases vaccines for half of the world's children and secures long-term funding from donors, helping create the visibility of demand and reducing the risk of investment for manufacturers. This helps to incentivize manufacturers to sustainably produce vaccines at prices that these countries can afford. And it works. As of 2018, it cost only USD 27 to immunize a child with a full course of basic vaccines in a Gavi-eligible country, compared to USD 1,300 in the US. It has helped to build healthier vaccine markets serving low-income countries: the number of manufacturers who supply Gavi with affordable vaccines has grown from five in 2000 to seventeen today, now that there is a viable developing country market.

EVERY DOLLAR INVESTED IN VACCINES YIELDS USD 54 IN WIDER SOCIETAL BENEFITS

THE SYSTEMS GOAL

Yet accessibility to vaccines relies not just on the affordability of the vaccines themselves, but on having strong systems in place to deliver them. This is where local and private sector partners play a crucial role in the work of the Alliance. Worldwide, 19.4 million children are still missing out on some vaccines: many of them in remote rural communities, urban slums, displaced communities or areas of conflict.[3] Gavi works with the private sector to harness new technologies that can address these bottlenecks. In Rwanda and Ghana, for example, fleets of autonomous drones are now being routinely used to avoid stockouts by delivering vaccines to communities across both countries when supplies are low or when there is unexpected demand. Developed by California-based technology company Zipline, and with support from the UPS Foundation and Gavi, these networks are supporting millions of people, increasing the reach of health services and reducing waste at the same time.

IMPACT

Since 2000, Gavi has helped protect more than 760 million children with vaccines against a range of diseases, and in doing so has prevented more than 13 million deaths. Coverage with the most basic vaccines has increased from 59% to 81% in Gavi-supported countries.[4] This has paid dividends not just in terms of lives saved but also in terms of helping to boost economies. In a Gavi-supported country, every dollar invested in vaccines yields USD 54 in wider societal benefits,[5] and since 2000 this has translated into more than USD 150 billion in economic gains. All this makes vaccines one of the most cost-effective public health interventions ever. At the same time, vaccines bring us closer to the goal of Universal Health Coverage, by acting as a platform that helps to strengthen primary health care, because vaccines don't deliver themselves. With vaccination comes infrastructure, supply chains, cold storage facilities, trained health care workers, community outreach, data services, disease surveillance, and much more. So, when communities get access to vaccination it puts these people on the map, and it is often not long before they also get access to a host of other critical services.

GAVI 5.0

Ultimately, Gavi is built on the philosophy that no-one should die of a vaccine-preventable disease, regardless of wealth, geography or gender. Yet every year 1.5 million people still do.[6] Reaching those still missing out will prove increasingly challenging, as population growth, rapid urbanization and climate change continuously move the goalposts. As will the unprecedented migration we are seeing with a record 70 million displaced people recorded last year. That is why Gavi's new strategy, its fifth, covering strategic period from 2021-2025, called Gavi 5.0, is prioritizing communities with zero dose children (children not received any routine vaccine doses) who have historically missed out on vaccines. It also recognizes the need to put gender more at the centre of our programmatic planning, to ensure that communities are engaged and to offer tailored support not just at the national level but also sub-nationally. This approach aims to reach an additional 300 million children by 2025, saving up to 8 million more lives. But also built into this plan is an understanding that many of the greatest global health challenges we will face are those that we cannot plan for. Climate change, antimicrobial resistance, and emerging infectious diseases pose an ever-evolving risk. As the threats to our health become increasingly globalized and increasingly unpredictable, the Vaccine Alliance provides a valuable opportunity to get a multitude of stakeholders around the same table. This has already enabled Gavi to help protect an entire generation of children. Efficiency, innovation and collaboration will be the names of the game going forward, to help us make further progress, protect the next generation, and ensure that by 2030 no one is left behind.

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REFERENCES

1. Kucharski A, Edmunds J. Case fatality rates for Ebola virus disease in West Africa. Lancet 2014; 384(9950):1260. Available from: https://doi.org/10.1016/S0140-6736(14)61706-2
2. World Health Organization. Ebola virus disease Democratic Republic of the Congo: external situation report 68/2019. https://www.who.int/publications-detail/ebola-virus-disease-democratic-republic-of-congo-external-situation-report-68-2019. [Accessed November 26, 2019].
3. World Health Organization. Immunization Coverage. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage [Accessed October 27, 2019].
4. World Health Organization. Immunization, vaccines, and biologicals. https://www.who.int/immunization/monitoring_surveillance/data/en/ [Accessed October 27, 2019].
5. ImmunizationEconomics.org. Decade of Vaccine Economics: return on investment. http://immunizationeconomics.org/dove-roi [Accessed October 27, 2019].
6. World Health Organization. Immunization. https://www.who.int/news-room/facts-in-pictures/detail/immunization [Accessed October 27, 2019].

SO FAR, 15 COUNTRIES HAVE TRANSITIONED OUT OF GAVI SUPPORT

The International Coordinating Group on Vaccine Provision

Vaccines are commodities for which ordinary market mechanisms do not apply. Their development including clinical testing, the production process, their shelf lives, and their often very limited supplier base, in combination with unpredictable disease outbreaks and epidemics, regularly lead to vaccine shortages. It is good to realise that vaccines are a public good and access needs to be equitable. From a public health point of view, national health authorities and international development partners need to ensure steady supplies and the efficient and fair distribution of scarce vaccines to places where they are needed most. With new vaccines entering the market and many parts of the world in civil or military turmoil, where outbreaks and epidemics thrive, reliable mechanisms for vaccine supply chain management are of paramount importance. Vaccination is a main pillar in emergency responses and disease outbreak management while the vaccine market has gradually become more complex. Ample supply is not a given anymore, e.g. only one manufacturer remains for the yellow fever vaccine. Ordinary lead times may be up to two years, shelf lives differ between different types of vaccines, and supply chain requirements have become more differentiated. Modern vaccines are very complicated in terms of production and quality control. As always, politics reign in this field as well, necessitating a fair public health approach which strives for equity and efficiency.
This article describes the role of The International Coordinating Group on Vaccine Provision (ICG) in ensuring that scarce vaccines are available where they are needed as part of disease control.

BACKGROUND

Triggered by an outbreak of cerebrospinal meningococcal meningitis in in 1996 in West-Africa, the ICG was established as the *International Coordinating Group on Vaccine Provision for Epidemic Meningococcal Disease*. The outbreak affected primarily Nigeria and Burkina Faso, with a total of 152,813 confirmed cases and 15,783 registered deaths. The actual incidence was probably considerably higher.

Since its establishment, the ICG has undergone several changes. In 2001 Yellow Fever (YF) vaccine was added to its mandate, followed by Oral Cholera Vaccine (OCV) in 2013. The ICG has three guiding principles:[1]

- Equity: distribution of vaccines based on public health priorities;
- Rapid and timely access: delivery of vaccines within a defined timeframe to control outbreaks;
- Independence: decisions made independently of political or economic influences, with the sole goal of improving public health.

Initially the ICG used a revolving fund to pre-finance the purchase of vaccines, vaccine-related supplies, and antibiotics. Countries were expected to reimburse the cost of vaccines drawn from the ICG stockpiles that were kept by manufacturers in their warehouses to enable replenishment. In 2002, the Gavi Alliance (see the article on GAVI elsewhere in this edition) started providing financial support, initially for the procurement of YF vaccine, later also of Meningitis vaccines (2008) and OCV (2013). At Gavi's request, the ICG stopped the reimbursement requirement for Gavi support-eligible countries in 2015. A year later, Gavi decided that investments in emergency vaccine stockpiles would no longer be time-bound and that non-Gavi-supported countries were also eligible to access vaccines from the stockpiles, in the understanding that they would ensure replenishment, with Gavi covering the financial risk in case they failed to do so.

The supply division of UNICEF plays a key role in this process, as it procures all the vaccines for the ICG stockpiles.[2] The revolving funds are now dormant, leaving the Gavi Alliance

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as the sole funding source for these stockpiles. Gavi also provides funding to support the operational costs of emergency immunization campaigns in Gavi-eligible countries.

financing, replenishment, monitoring, and reporting. In 2015, discussions started about an ICG mechanism for a future Ebola vaccine.[3] An ICG Ebola expert group is not in place though.

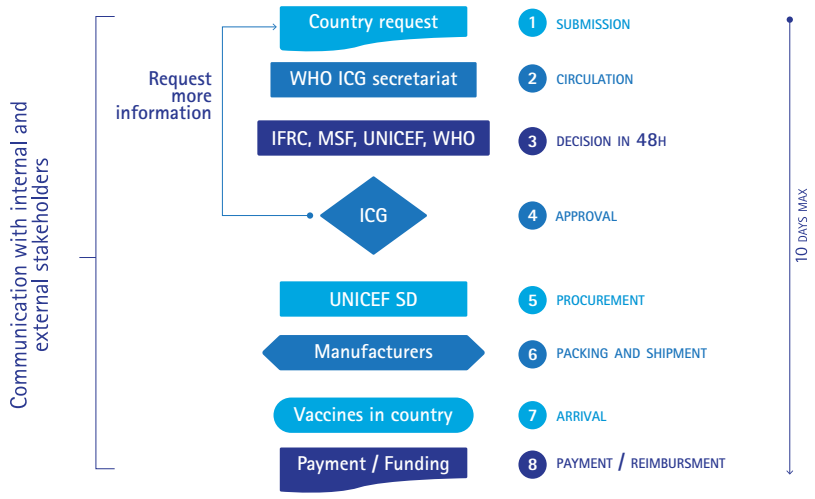

Figure 1: The ICG mechanism (Adapted from: http://www.who.int/csr/disease/icg/qa/en/).

The ICG Executive sub-Group is constituted by its 4 founding members: WHO, UNICEF-Headquarters, *Médecins Sans Frontières* (MSF), and the International Federation of Red Cross (IFRC). Other stakeholders, such as UNICEF's Supply Division (Copenhagen), *Agence de Médecine Préventive* (AMP), Centre for Disease Control, manufacturers, international NGOs, technical agencies, financial partners and country representatives (two from countries in the African meningitis belt, plus a third country) support various activities of the ICG mechanism, e.g. decision-making, forecasting of vaccine requirements, procurement, and deployment. The ICG Executive sub-Group reviews requests not only from countries but also from international organisations that act swiftly in the event of disease outbreaks such as MSF. It can do so within 48 hours after receipt by its secretariat of a formal request.

Standard operating procedures for emergency stockpiles of meningitis and YF vaccine (but not for OCV) are in place for vaccine applications, release,

The full ICG meets physically twice a year as well as through remote digital conferencing in the event of an emergency request. The ICG Secretariat based at WHO-HQ plays a central and coordinating role in the entire ICG mechanism. It also does price negotiations through its constituency and network, and evaluates interventions and standard protocols for managing vaccine-preventable diseases. Its informality and flexibility is a key strength. Vaccines are allocated based on technical and public health criteria without political or financial considerations. The ICG mechanism is depicted in Figure 1. It aims at delivering vaccines within a time span of a maximum of 10 days after receipt of the request.

Recent major outbreaks – yellow fever in DR Congo and Angola, cholera in Yemen and the Horn of Africa – have confirmed the need for effective management and distribution of vaccines of which the supply can be unreliable. In 2017 for example, the ICG had to prevent Angola from procuring large quantities of YF-vaccine that would have left the border area in DRC exposed to further spread of the epidemic. The criteria used during decision-making differ among the three stockpiles because each outbreak has its own peculiarities. These criteria are publicly available. [4,5,6] The balance between responding to single outbreaks and considering the global epidemic context is and remains delicate. When working in epidemic or outbreak settings, public health experts should be aware of ICG's existence and its modus operandi so they can act and advise in an appropriate manner.

THE GLOBAL DISEASE CONTROL CONTEXT

The occurrence of and response to disease outbreaks need to be seen in the context of global disease control strategies. In many cases outbreaks are the consequence of insufficient coverage of routine immunisation systems and failure to compensate for that with effective special immunization activities, including campaigns. While ministries of health with the support of various partners usually implement control programmes for meningitis, YF and cholera through routine preventive and reactive immunisation, it is the ICG that coordinates the management of the three vaccine stockpiles, especially in emergency outbreak situations.

1. CHOLERA

In 2013, WHO established the Global Oral Cholera Vaccine (OCV) stockpile, and the Global Task Force on Cholera Control (GTFCC) launched a renewed strategy for cholera control in which OCV plays an important role. [7] Many countries are now integrating the use of OCV within their cholera control programs. As of May 2018, over 25 million doses had been administered in 19 countries – of which 41% in humanitarian situations, 38% for outbreaks, and 21 % for endemic areas.

2. YELLOW FEVER

The Yellow Fever Initiative was launched in 2006 as a joint collaboration of WHO and UNICEF. In 2016, a new more specific and comprehensive strategic approach towards the Elimination of Yellow fever Epidemics (EYE) was

developed.[8] It involves a mechanism that automatically replenishes the emergency stockpile to ensure that 6 million doses are available at all times. The ICG remains responsible for rapid and independent decision-making on the allocation of YF vaccines during emergencies.

3. MENINGITIS

There is no single strategy that combines prevention, routine immunisation, and emergency responses for meningitis. At present the supply of serogroup A meningococcal conjugate vaccine (MenAfriVac) is adequate and affordable, which has helped substantially to reduce the number and severity of meningitis outbreaks in countries of the African meningitis belt. However, meningitis outbreaks are now dominated by other meningococcal serogroups, for which conjugate vaccine supplies are insufficient and expensive.

4. EBOLA

The recent approval of an Ebola vaccine following outbreaks in West-Africa and the eastern part of the Democratic Republic of Congo (DRC) shows that there is political will and funding to develop new vaccines in a much shorter time that ever before. An important milestone in 2015 were the trials in which more than 16,000 volunteers in Africa, Europe and the United States received the rVSV-ZEBOV vaccine. The vaccine was found to be safe and to offer protection against the Ebola virus. Following further testing during Ebola outbreaks in DRC/Equateur province (in May-July 2018) and DRC/North Kivu province (still ongoing) and consultations by the Strategic Advisory Group of Experts on Immunization (SAGE), the Ebola vaccine was formally approved and licensed by WHO in November 2019, just before this paper went to press.[9] It means that the vaccine can now widely be used, rather than under certain restrictions ('expanded access' or what is also known as 'compassionate use'). Ringfencing vaccination in combination with early case detection and widespread vaccination of health staff working in outbreak situations will certainly boost demand. Considering the experience with bivalent polio vaccine, which was in short global supply for some time, undermining the smooth implementation of the global polio eradication strategy, it remains to be seen whether industry can meet the future demand for Ebola vaccine.

CONCLUSION

Since infectious agents can spread faster than ever after an outbreak, even from very remote areas, vaccine-preventable disease control is of global public health importance. Both management and financing of vaccine development and supply need to be secured through close coordination of all stakeholders: national authorities, international health organisations, international and national NGOs, and the vaccine manufacturing industry. The ICG, with its secretariat based in WHO headquarters, plays a key role in monitoring and guiding vaccine provision. Its mandate and capacity need to be safeguarded, free from any (geo)political interference. While comprehensive and adequate mechanisms are in place for the three vaccines discussed above that fall within ICG's mandate, the recent approval of an Ebola vaccine shows that there is political will and funding to develop new vaccines in a much shorter time that ever before. It is opportune to now also safeguard the provision of Ebola vaccine. The ICG could fulfil that role.

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REFERENCES

1. World Health Organization: Review of the International Coordinating Group on Vaccine Provision, 2006-2016. WHO Geneva, 2016
2. www.https://www.unicef.org/supply/
3. International Coordinating Group for Ebola Vaccine, 1st Meeting, 11 December 2015 – WHO Headquarters, Geneva, Switzerland
4. Meningitis guidelines: http://apps.who.int/iris/bitstream/10665/154595/1/WHO_HSE_GAR_ERI_2010.4_Rev1_eng.pdf?ua=1
5. Yellow fever guidelines: http://www.who.int/csr/disease/icg/ICG-request-form-EN.pdf?ua=1
6. OCV guidelines: http://www.who.int/cholera/vaccines/Briefing_OCV_stockpile.pdf?ua=1
7. https://www.who.int/cholera/task_force/en/
8. https://www.who.int/csr/disease/yellowfev/eye-strategy-and-global-agendas/en/
9. Burki T. Ebola virus vaccine receives prequalification. Lancet 2019; 394(10212):1893. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32905-8/fulltext?dgcid=raven_jbs_etoc_email

CALL FOR ARTICLES

Following a request from several NVTG working parties earlier this year, we hereby call for contributions to next year's editions of MT*b*. The Editorial Board is planning to cover the following themes:

- Disease modelling
- Mental health
- Orphan diseases
- Global Health education
- Support to church affiliated hospitals in sub-Saharan Africa: past and present

We would be pleased to receive your contributions – in relation to these themes or any other topic – in the form of an article, news from the working party in which you are involved, a letter from the field, a personal viewpoint, or an ethical dilemma that you have come across.

The Editorial Board

Monitoring of vaccine preventable diseases in the Netherlands

The example of maternal pertussis vaccination

Pertussis, or whooping cough, is a bacterial infection of the respiratory tract. After the introduction of mass vaccination in the 1950s, the bacteria seemed to have disappeared, but in the 1990s pertussis re-emerged despite the high vaccination coverage rates, mostly affecting very young infants who are not yet (fully) vaccinated (Figure 1).[1,2] In an effort to address this problem, Tdap (tetanus, diphtheria and acellular pertussis) vaccination for pregnant women, also called the maternal pertussis vaccination, was introduced in the USA in 2011 and in England a year later.[3] Many European countries followed soon after that. By inducing the transfer of antibodies from mother to child through the placenta, the vaccine provides protection of the new-born child until it gets its first vaccination.[3]

The resurge of pertussis also happened in the Netherlands. Tdap vaccination for pregnant women was introduced following an advice by the national health council in 2015, but it was not free of charge and the vaccine has not always been available. In December 2019, maternal pertussis vaccination will be added to the Dutch national immunisation programme (NIP).

The safety and effectiveness of all vaccinations in the Netherlands, including maternal pertussis vaccination, is monitored by the Centre for Infectious Disease Control (CIb, part of the National Institute of Health and the Environment (RIVM)) together with the pharmacovigilance centre Lareb. Surveillance of diseases included in the NIP consists of mandatory notifications and monitoring of laboratory and hospital admission data. Other 'pillars' include vaccination uptake, adverse events surveillance, pathogen surveillance and immunosurveillance (Figure 2).[4,5] Here we illustrate these five pillars with the example of maternal pertussis vaccination.

VACCINATION UPTAKE

Vaccination coverage is assessed yearly and reported in the annual vaccination coverage report, using the individually based vaccination registration system Praeventis.[6] After a small decrease in the period 2012-15, full vaccination coverage of 2-year old children stabilized at around 90%. With the implementation of maternal pertussis vaccination, a new target group has been added to the NIP: all pregnant women are eligible and those who are actually vaccinated under the pregnant women (the enumerator) are registered in the NIP register of Praeventis. All pregnant women who deliver in a certain year in the Netherlands (the denominator) are registered in a special perinatal register called Perined.[7]

Acceptance of vaccination is periodically assessed through qualitative studies.[4] A recent study (unpublished), carried out in 2018-19 among pregnant women and mothers of children below the age of two, assessed knowledge about maternal

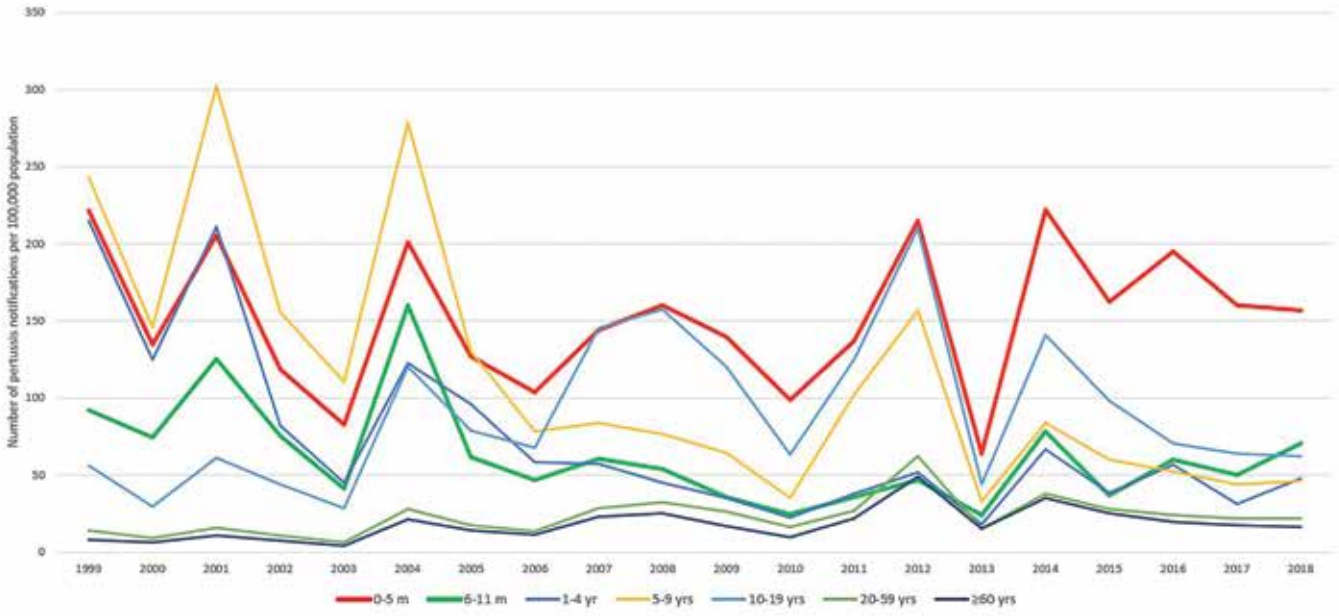

Figure 1: Pertussis incidence in the Netherlands stratified by age group, 1999-2018.

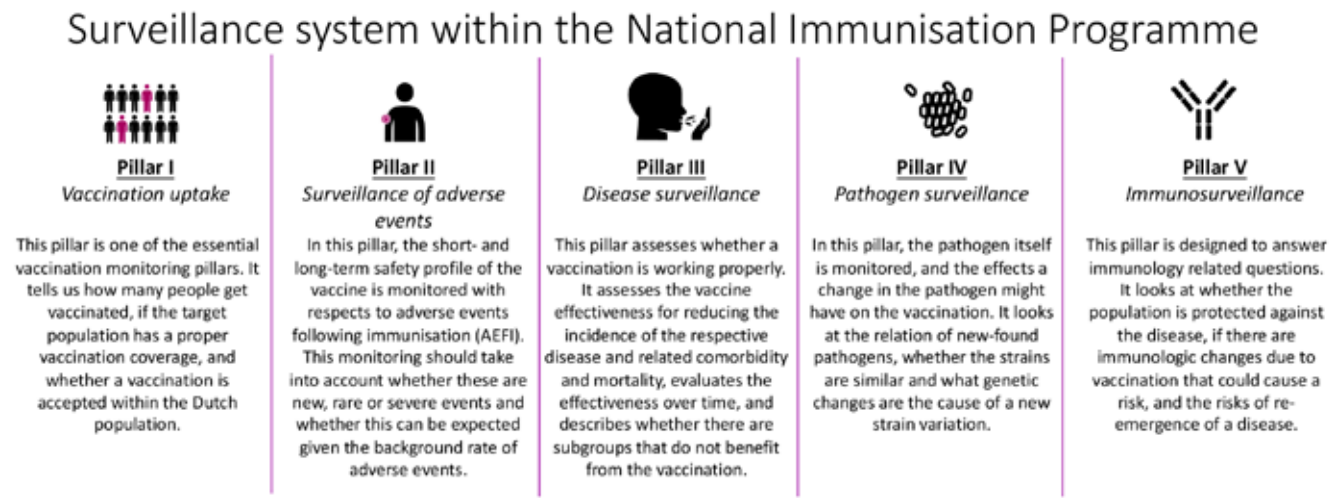

Figure 2: Five pillars of NIP surveillance in the Netherlands.[5]

pertussis vaccination and willingness to vaccinate. It showed that 70% of the women had heard or read about maternal pertussis vaccination, and 60% of pregnant women had the intention to get vaccinated. The most common reason among women who had already given birth to refrain from vaccination was lack of information: when they were pregnant they did not know that this was an option. Most pregnant women interviewed indicated a high level of trust in the information provided by their midwives, consultation centres and RIVM (78%, 70% and 79%, respectively).

SAFETY SURVEILLANCE

Safety surveillance is important to assess the nature and frequency of adverse events in order to ensure the population does not mistrust the NIP. This pillar relies on a passive reporting system of adverse events following immunisation (AEFI), in place at the centre for pharmacovigilance in the Netherlands, Lareb. Both professionals and the general public can report AEFIs. It is important to bear in mind that reported events do not necessarily have a (proven) causal link to vaccination. The influence of media attention on such reporting should not be underestimated. When notable signals are observed, Lareb performs a causality assessment and decides what is more likely: a causal relation with the vaccination or a coincidental signal. Regarding maternal pertussis vaccination, safety studies and reviews show that maternal pertussis vaccination is safe. No adverse pregnancy outcomes, such as stillbirth or neonatal death were reported.[3,8-10] After implementation of maternal pertussis vaccination, safety monitoring will also be performed in the Netherlands to provide relevant information to the public.

DISEASE SURVEILLANCE

Besides monitoring of hospital admissions and mortality attributed to vaccine-preventable diseases, disease surveillance involves mandatory notifications. WHO also requires notification (annually), and there is an exchange of information on the occurrence of several diseases (e.g. diphtheria, tetanus, poliomyelitis, pertussis, mumps, measles, rubella, hepatitis B, and meningococcal disease) with other European countries through the European Surveillance System (TESSy) of the European Centre for Disease Control (ECDC).[11] Differences in incidence between countries, considering their vaccination programme and history, are evaluated to optimize vaccination impact and better identify high-risk groups.

The maternal pertussis vaccination will be implemented in the Netherlands because of the high incidence of pertussis in new-born children (Figure 1) combined with a good vaccine effectiveness. Vaccine effectiveness (VE) in the Netherlands is usually assessed through a screening method developed by Farrington.[12] For the calculation of the VE of maternal pertussis vaccination, the coverage of a certain age cohort and the difference in pertussis incidence between vaccinated and unvaccinated children below 3 months of age is needed.

THE MATERNAL PERTUSSIS VACCINATION WILL BE IMPLEMENTED IN THE NETHERLANDS BECAUSE OF THE HIGH INCIDENCE OF PERTUSSIS IN NEW-BORN CHILDREN

PATHOGEN SURVEILLANCE

RIVM studies the possible adaptation of the *Bordetella pertussis* bacteria based on samples provided by medical microbiology laboratories. It involves antigen expression validation assays to determine pertussis antigens: pertussis toxin (Ptx), pertactin (Prn), and filamentous hemagglutinin (FHA). A high frequency

of pathogens that are deficient in one of these genes could predict vaccine evasion, which might lead to a pertussis outbreak.[4] Recently, whole genome sequencing was introduced, which can detect even smaller strain differences and changes. A change in the pertussis strains due to the maternal pertussis vaccination is not expected, as the vaccination protects against the same strains as the vaccination during childhood.

IMMUNOSURVEILLANCE

Protection against disease can be assessed by measuring antibody levels (seroprevalence). Seroprevalence studies enable the identification of susceptible population groups that are at risk of infection, and provide a standardized value to compare countries. Serosurveillance in the Netherlands, also called immunosurveillance, is done by the RIVM/CIb. They periodically collect blood samples and demographic data from a representative sample.

The immunologic effects of the maternal pertussis vaccination were measured in the Maternal Immunisation Pertussis (MIKI) study at the RIVM/CIb, which concluded that infants of women who obtained maternal pertussis vaccination could be vaccinated twice, at 3 and 5 months, instead of three times (at 2, 3 and 4 months).[13] The Premature Infants and Maternal Pertussis Immunisation (PIMPI) study, also conducted by RIVM/CIb, assesses the immunologic effects of maternal pertussis vaccination in premature infants, and the effect that timing of this vaccination has on antibody transmission from mother to child. Research on the immunologic effect of maternal pertussis vaccination in other countries has shown an increase in antibody levels during the first months of life in children whose mother had been vaccinated. Furthermore, several studies reported a lower immune response after the first dose of infant vaccination when the mother had been vaccinated during pregnancy. This is called 'blunting'.[10,14] Recent research has shown no clinical relevance for the blunting effect, and confirmed that maternal pertussis vaccination offers protection against pertussis.[10,15]

FUTURE PERSPECTIVE

Given the rapid development of new vaccines, the ever-changing epidemiology of vaccine preventable diseases, and new scientific evidence that has implications (e.g. for vaccination schedules), close monitoring of NIP performance is crucial. When a new vaccination is introduced, RIVM takes charge of the necessary surveillance. With the five pillars of the Dutch surveillance system in place, all elements of surveillance of vaccine preventable diseases are covered, safety and effectiveness are closely monitored, and cross-border communication and data-sharing is happening.

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REFERENCES

1. Van der Maas NA, Mooi FR, de Greeff SC et al. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? Vaccine. 2013;31(41):4541-7.
2. Mooi FR, Van Der Maas NA, De Melker HEJE. Infection. Pertussis resurgence: waning immunity and pathogen adaptation–two sides of the same coin. 2014;142(4):685-94.
3. Gkentzi D, Katsakiori P, Marangos M et al. Maternal vaccination against pertussis: a systematic review of the recent literature. Arch Dis Child Fetal Neonatal Ed. 2017;102(5):F456-F63.
4. RIVM. The National Immunisation Programme in the Netherlands: Surveillance and developments in 2016-2017. National Institute for Public Health and the Environment; 2017.
5. Van der Maas NA. Vaccine-preventable diseases: evaluation of vaccination programmes and optimisation of surveillance. Zeist, The Netherlands 2018. 16-8 p.
6. RIVM. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2018. Rijksinstituut voor Volksgezondheid en Milieu; 2019.
7. Perined. Perinatale Zorg in Nederland 2017. Utrecht: Perined; 2019.
8. Donegan K, King B, Bryan PJB. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ 2014;349:g4219.
9. Munoz FM, Bond NH, Maccato M et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA. 2014;311(17):1760-9.
10. Campbell H, Gupta S, Dolan GP et al. Review of vaccination in pregnancy to prevent pertussis in early infancy. J Med Microbiol. 2018;67(10):1426-56.
11. Surveillance atlas of infectious diseases ECDC: ECDC; 2017 [Available from: https://www.ecdc.europa.eu/en/surveillance-atlas-infectious-diseases.
12. Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J Epid. 1993;22(4):742-6.
13. Barug D, Pronk I, van Houten MA et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. Lancet Infect Dis. 2019;19(4):392-401.
14. Maertens K, Caboré RN, Huygen K et al. Pertussis vaccination during pregnancy in Belgium: results of a prospective controlled cohort study. Vaccine. 2016;34(1):142-50.
15. Becker-Dreps S, Butler AM, McGrath LJ et al. Effectiveness of prenatal tetanus, diphtheria, acellular pertussis vaccination in the prevention of infant pertussis in the U.S. Am J Prev Med. 2018;55(2):159-66.

FULL VACCINATION COVERAGE OF 2-YEAR OLD CHILDREN STABILIZED AT AROUND 90%

Vaccine hesitancy: a new kid on the block

Vaccination is one of the most effective public health interventions, and one that prevents 2-3 million deaths worldwide every year.[1] In 2018, 86% of all eligible infants in the world received at least one dose of measles vaccine and 69% received the second dose, leaving around 20 million children who did not receive any dose. Also about 86% of infants worldwide (116.3 million infants) received their third dose of diphtheria-tetanus-pertussis (DTP), with 129 countries achieving at least 90% coverage [2] These are tremendous achievements. However the health gains achieved by the success of vaccination programmes are under threat. The rise in the incidence of measles, especially observed in Europe and North America, the 2015-16 outbreak of yellow fever in Angola, and two new cases of polio in the Philippines can be directly linked to a decrease in vaccine coverage in these countries. They illustrate the challenges we face in protecting citizens against the threat of vaccine-preventable diseases. There is a tendency for people to delay in accepting or even refusing vaccination altogether, despite the widespread availability of vaccination services. This is referred to as vaccine hesitancy. The most important determinants are individual choices and group influences, combined with specific features of certain vaccines and vaccination-related issues and often aggravated by contextual factors.[3]

Maintaining high vaccination coverage levels to protect the population requires a permanent commitment by those delivering, monitoring, and funding vaccination programmes. Poor vaccination uptake may reflect changing societies with shifting values and preferences, greater mobility of people, and changing vulnerabilities. But there are also issues of communication and deliberate attempts to undermine the success of vaccination by so-called *´anti-vaxxers´*. They spread and take advantage of public fears about the safety of vaccination. How to deal with these challenges?

THE QUESTION IS: HOW DO PEOPLE MAKE THEIR DECISIONS?

BETTER UNDERSTANDING OF DETERMINANTS OF VACCINATION ACCEPTANCE

People feel the need to make an informed and deliberate decision pro or contra vaccination for themselves or their children, but they often feel unable to do so based on the available information. Information provided by health authorities is perceived as too limited or biased. Information available on the internet is often unbalanced and does not give the full picture. Parents of young children do not always consider the information provided by health professionals as satisfactory, with some arguing that it is not designed to inform but to induce conformity. Other factors that play a role for people to accept or refuse vaccination include personal convictions, for instance after some bad experience with vaccination or a disease, psychosocial determinants (e.g. risk perception, feelings of loss of control, or decisional uncertainty), and pragmatic reasons (e.g. time constraints, inconvenient location, or limited provider choice). So the question is: 'How do people make their decisions on whether or not to accept specific vaccinations?' While there is an abundance of literature on how people make personal choices in their lives, little research has been conducted on decision making regarding vaccination.

A MORE SYSTEMATIC APPROACH TO COMPREHENSIVE VACCINATION PROGRAMME DEVELOPMENT

Until recently, most vaccination programmes had an information and education component, using various channels (individual letters, posters, group meetings, etc.), and they offered various service options (e.g. vaccination on appointment). With the advent of the internet, this appears to be no longer sufficient. A modern successful vaccination programme needs to be based on a good understanding of the enablers and the barriers to vaccination acceptance and include an effective translation of behavioural change methods into practice. Careful planning with relevant stakeholders in various stages of a vaccination programme is a must. It starts with answering questions such as 'What is the problem?' and 'For whom is this a problem?', followed by the question 'Which determinants could influence vaccination acceptance?' Subsequently, it is important to discuss how to achieve the programme goal by answering a question like 'Who has to do what in order to promote vaccination under the target group?' Next, the most relevant and amenable determinants have to be selected. In the third step, a strategy can be designed by arranging all change objectives by determinant and identifying theoretical methods which are potentially applicable for that determinant in order to achieve the change objective. Feasibility and possible fit of the practical applications of these methods with the needs and intervention context of the target group are essential. Integration of the various elements that were chosen in the previous step will lead to a concrete approach containing, for instance, a personal invitation letter, an information folder or website, and a deliberation tool.[3]

Once a vaccination programme has been developed, implementation must guarantee improved access to vaccination and provide different sectors of the healthcare workforce with adequate resources. They must be able to deliver

a high-quality vaccination programme that develops data solutions to enable individuals to demonstrate their vaccination status regardless of where they are and that provides clear messages on the evidence for vaccination. Vaccination programme monitoring must also help to identify groups and communities that are most underserved in order to vaccinate them.

DIALOGUE

Community engagement is key to successfully controlling infectious disease outbreaks. That is not only and once again the lesson learned in the recent Ebola virus disease outbreak in DRC; it also applies to vaccination campaigns in general. The best chances for overcoming low coverage rates are through a respectful and extensive dialogue with target groups, in particular when misconceptions, religious arguments, or mistrust of authorities dominate.[4] A similar approach is needed towards the debate on voluntary versus mandatory vaccination policies, whereby sufficient attention should be paid to what people in concrete societal contexts think and feel about these themes. A strained relationship between health authorities, service providers and the general public could be detrimental to the success of vaccination programmes, as its success depends on people's continued trust and acceptance.

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REFERENCES

1. https://www.who.int/immunization/newsroom/new-measles-data-august-2019/en/
2. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage
3. Visser O. Preventing pertussis in early infancy – Developing of a strategy for implementing pertussis vaccination of new parents and health care workers. PhD dissertation, Nijmegen, Radboud Institute of Health Sciences, 2018.
4. Ruijs H. Acceptance of vaccination among orthodox Protestants in the Netherlands. PhD dissertation. Nijmegen, Radboud Institute of Health Sciences, 2012.

Vaccination: who is best equipped in the era of postmodern mistrust?

Public health is a science and profession with an impressive track record. It saved mankind from the horrors of smallpox and helps in preventing diseases and avoiding all kinds of health hazards. The Netherlands is currently going through a period of declining vaccination rates. Vaccination against human papillomavirus (HPV) as well as Herpes Zoster and Rotavirus is met with great suspicion and has become controversial, even among some health professionals.

In the public debate, the confidence in public health authorities is being questioned. There is a great deal of mistrust by a seemingly growing number of people, some of whom allege that the interest of the population at large seems to prevail over that of the individual. Some of the so-called 'anti-vaxxers' believe that measles vaccination may cause autism, pointing their fingers at the pharmaceutical companies for ignoring such claims. These perceptions are difficult to combat. Drastic solutions like making vaccination obligatory may help a bit, as well as improving patient-centred counselling, but they do not fundamentally tackle the root of the problem.

The underlying problem is predominantly mistrust. We, the Working Party for Family Physicians and International Health (in Dutch: WHIG), recommend that people who have a medical condition obtain their vaccination from their family practice. Family Physicians (FPs) in the Netherlands are independent professionals who provide continuous integrated care. They are expected to adhere to guidelines established by their professional organization (NHG, the Dutch College of General Practitioners). The fact that they are seen as independent creates trust among their patients, which justifies a stronger role for FPs in the provision of vaccinations.

For other public health activities, such as the provision of flu vaccination and cervical cancer screening, FPs receive a decent financial compensation and this has resulted in high coverage rates. This shows that general practices are already an appropriate place of choice for vaccination of specific target groups, including patients with some kind of health conditions (immune suppression, chronic diseases). In case patients are hesitant to get vaccinated, FPs commonly use instruments such as counselling and shared decision making. The benefits of vaccination need to be weighed against someone's resistance to perceived intrusion or loss of body integrity. Sometimes people are even challenged to give up their religious principles against vaccination.

THE INTEREST OF THE CLIENT SHOULD PREVAIL WHEN DECIDING WHO IS BEST PLACED TO PROVIDE VACCINATION SERVICES

Ideally, vaccination should be considered a positive choice, weighing the public interest of protecting society (as in the case of measles) against an individual's desire for autonomy. Unless public health practitioners lend an ear to people's concerns and objections and unless parents who worry about the possible side-effects of vaccination for their young children are taken seriously, popular support for vaccination will dwindle.

We as FPs postulate that some of the current policies inhibit optimal service provision and are not as effective as one would wish. Some examples:

- As family physicians and members of WHIG, we strongly believe in the benefits of travel advice in general practice as a low-threshold service for people intending to travel abroad. Many travelers go on holiday insufficiently vaccinated or counselled on other preventive measures. This is true in spite of the availability of excellent scientific advice from the LCR (National Coordination Centre for Travel Advice). Precisely here a FP can make a difference. We think it is a missed opportunity that FPs are not facilitated in providing travel advice services. This is also becoming increasingly relevant, as many (elderly) people with chronic conditions undertake trips that are not without risk. Certain occupational health services (KLM, etc.) and specialist clinics are undisputedly more specialized in providing travel advice than FPs. However, FPs have the advantage of having a long-term relation with their clients and being more familiar with their family situation, which is all the more relevant in case people return from abroad with an illness.
- In the HPV vaccination campaign, girls at the sensitive age of 13 years often received their shot in a sports hall, with several of them crying and giving the creeps to other girls. The logistics were technically safe, but the circumstances were rather off-putting for young girls. Such an impersonal approach may be necessary for a serious disease outbreak but not in this case. Why not opt for the intimacy of the general practice? Most practices can easily handle the relatively small numbers involved in an inexpensive manner, integrating this type of vaccination into their daily routine. Because of their personal relation with their clients, FPs are perfectly capable of managing girls' (and boys') and parents' mistrust, if any.
- For flu vaccination, it seems logical that multiple target populations are served by different care providers. Occupational health services offer vaccination to employees, but often with disappointing vaccination rates of below 50%. Inviting employees to get vaccination from their FPs, with whom they can discuss vaccine requirements, could result in a better coverage.
- Future vaccines for pneumococci and herpes zoster could also best be administered by FPs.

The interest of the client should prevail when deciding who is best placed to provide vaccination services. That seems common sense. The Dutch health care system has become a marketplace since 2006, with quite some competition, commercial interests, fragmentation, and incoherence. This has caused confusion and undermined the public's confidence, leading to suboptimal vaccination rates. FPs are best placed to maintain and update their clients' personal medical files, including their vaccination status. For children below five years of age, the national vaccination programme (RVP) in the Netherlands is well established and effective. However, for adult vaccination programmes, there is no overarching policy of the Dutch government on who should be in the lead or do what. The Ministry of Health (VWS) seems to rely on free market forces. There is a divide between the municipal health services (GGD) and general practitioners, which is a tragic flaw of our (privatized) health system. In national health services of countries like the UK, Portugal and Spain, this is not so much the case. The divide in the Netherlands not only affects the organisation of adult vaccination but also cripples other preventive health measures.

Accepting that general practices run by FPs are an appropriate platform for providing comprehensive health services is in the clients' interest and may eventually be the most (cost-) effective strategy to provide vaccination and other preventive measures. We hope that the Dutch College of Family Health Physicians (NHG) and the Association of FPs (LHV), the National Institute for Public Health and the Environment (RIVM), the Netherlands Institute for Control of Infectious diseases (NIVB), and patient interest organisations will endorse our plea.

Note: another article, in Dutch, on the same topic was recently published by Pieter van den Hombergh and Ted van Essen, under the title 'De huisarts heeft de beste papieren om te vaccineren' (Medisch Contact 46, 14 november 2019).

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IN MEMORIAM

Wouter W.E. Nolet
M.D. Global Health and Tropical Medicine

On the 23rd of November 2019, Wouter passed away at the age of 32, due to the complications of Lassa fever.

We are shocked by the loss of a devoted professional and, for many, a dear friend. During his Global Health and Tropical Medicine training, Wouter was a highly involved and much appreciated board member of TROIE and Consult Online. After his training, he worked as Programme Coordinator for CapaCare in Sierra Leone. His versatile role included training Masanga's Community Health Officers and aspiring Global Health doctors.

With his many qualities and numerous endeavours, Wouter's personality and life are impossible to capture in a few words. His smile was heart-warming, his choices an inspiration, and his life exemplary. We will miss him dearly.

We wish his family, partner and friends strength; our thoughts are with them.

On behalf of TROIE, Consult Online, MTb and NVTG

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