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Vaccines, inspiring innovation in health ☆

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ABSTRACT

This report covers the topics of pandemics, epidemics and partnerships, including regulatory convergence initiatives, new technologies and novel vaccines, discussed by leading public and private sector stakeholders at the 18th Annual General Meeting (AGM) of the Developing Countries Vaccine Manufacturers' Network (DCVMN). Contributions of Gavi and the vaccine industry from emerging countries to the growing global vaccine market, by improving the supply base from manufacturers in developing countries and contributing to 58% of doses, were highlighted. The Coalition for Epidemic Preparedness Innovations (CEPI), the International Vaccine Institute (IVI) and others reported on new strategies to ensure speedy progress in preclinical and clinical development of innovative vaccines for future MERS, Zika or other outbreak response. Priorities for vaccine stockpiling, to assure readiness during emergencies and to prevent outbreaks due to re-emerging diseases such as yellow fever, cholera and poliomyelitis, were outlined. The role of partnerships in improving global vaccine access, procurement and immunization coverage, and shared concerns were reviewed. The World Health Organization (WHO) and other international collaborating partners provided updates on the Product, Price and Procurement database, the prequalification of vaccines, the control of neglected tropical diseases, particularly the new rabies elimination initiative, and regulatory convergence proposals to accelerate vaccine registration in developing countries. Updates on supply chain innovations and novel vaccine platforms were presented. The discussions enabled members and partners to reflect on efficiency of research & development, supply chain tools and trends in packaging technologies improving delivery of existing vaccines, and allowing a deeper understanding of the current public-health objectives, industry financing, and global policies, required to ensure optimal investments, alignment and stability of vaccine supply in developing countries.

1. Introduction

The 18th Annual General Meeting of the Developing Countries Vaccine Manufacturers' Network (DCVMN) gathered over 270 vaccine experts from 38 member-companies in emerging countries, 23 non-member companies and 28 non-industry organizations to inspire innovation and promote global access to vaccines. The meeting, hosted by SK Chemicals and co-hosted by the International Vaccine Institute (IVI) in Seoul, South Korea, focused on pandemics, epidemics and partnerships.

DCVMN President, M. Datla, opened the meeting, noting the increase in global uptake of vaccines over the 18 years of DCVMN's existence. J. Ahn welcomed attendees and expressed SK Chemical's commitment to healthcare and resolution of tackling pressing public-health issues through innovation and partnerships. Korean Deputy Minister of Health and Welfare, D. Kwon, emphasized that vaccines are part of the social security of Korea and described efforts to expand support for vaccines [1].

S. Berkley reported that immunization coverage of DTP[2]-containing vaccines has increased by 20%-points since the launch of Gavi support for poorest countries [2]. The vaccine supply base has grown from 5 manufacturers in 5 countries in 2001 to 15, in 11 countries, in 2016. The role of DCVMN manufacturers in vaccine supply is illustrated in Figure 1. While the impact of increased vaccination coverage has been substantial [3,4], still 19.5 million

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[1] Mahima Datla, Steven Gao, Akira Homma, Deborah Hong, Suresh Jadhav, Ikjung Kim, Jerome Kim, Fernando Lobos, Jin Park, Sai Prasad, Alexander Precioso, Patrick Tippoo, Lingjiang Yang.

[2] Diphtheria Tetanus Pertussis

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0264-410X/

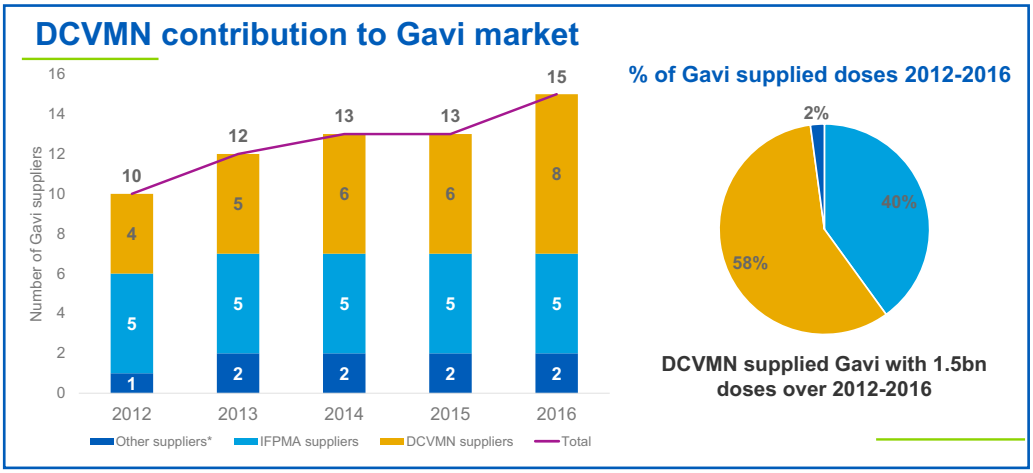

Fig. 1. DCVMN contribution to Gavi market. The critical role of DCVMN in ensuring high proportion of vaccine availability in number of doses (pie chart) to Gavi countries. The growing number of manufactures supplying Gavi (columns chart) from emerging countries is illustrated by yellow bars, as compared to vaccine manufacturers from industrialized countries, light blue bars, and other regions, dark blue bars. Courtesy of S. Berkley, Gavi. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

newborns annually do not receive basic vaccines [5]. Gavi's role in outbreak preparedness and response is also growing through maintaining stockpiles of yellow fever, measles and cholera vaccines and investing in additional key vaccines, such as Ebola. A recent project supported the introduction of Eubiologics' new oral cholera vaccine to Gavi countries.

2. Vaccine procurement and financing

T. Cernuschi, WHO, noted that self-procuring, middle-income countries need better information on available products, suppliers, demand and supply forecasts and pricing information to improve decision-making and the management of vaccine shortages [6]. The WHO's Vaccine Price, Product, and Procurement platform addressed this gap by collecting vaccine pricing data from 144 countries (Fig. 2) [7]. The initiative aims to inform global supply policies and strategies. It is also involved in global dialogue facilitated by The Humanitarian Mechanism, launched this year to facilitate timely access to and affordability of vaccines during humanitarian emergencies.

S. Rautio outlined UNICEF's stockpiling strategies, priorities and forecasting, funding and contracting activities [8]. UNICEF procures around 2.5 billion doses of 40 WHO-prequalified vaccines and distributes these to around 100 countries, managing demand and reallocating supply to level-out fluctuations and avert crises. Since 2010, UNICEF has responded to around 300 humanitarian situations in 90 countries annually, with a peak in 2016 (Fig. 3). For bivalent oral poliovirus vaccine (bOPV) in 2017, a rolling buffer of 150 million doses is maintained, with a further 115 million doses of bulk maintained by manufacturers, ready for delivery within 3 months. A unique challenge is presented by the OPV type 2 stockpile, established to support the Global Polio Eradication Initiative (GPEI) should type 2 outbreaks occur following the withdrawal of trivalent OPV. The same will apply to OPV types 1 and 3, to be secured after future bOPV cessation.

R. Rustan provided an overview of BioFarma's supply of bOPV and polio vaccine bulk over the last five years and estimates for supply from 2018 to 2021, for both routine and supplementary immunization. Development of Sabin IPV is progressing and a bulk stockpile of monovalent OPV type 2 is being established in collaboration with the GPEI.

I. Lewis, UNICEF, reviewed the expected increase in the inactivated polio vaccine (IPV) availability in 2018. Offers have been received from more than 10 manufacturers for the IPV tender of 2019–2022.

L. Meng mentioned the China National Biotechnology Group's Sabin IPV vaccine, licensed in 2017, and its plans to produce 10 million doses by the end of 2017 to meet domestic market needs. There is also a pipeline of Sabin IPV vaccines at the Wuhan site, Sinovac and Minhai Biotechnology. After 2020, China will have excess IPV capacity available for the international supply.

S. Zipursky updated the audience on the WHO-Polio Endgame, as wild poliovirus continued to be transmitted in Pakistan and Afghanistan in 2017, and six vaccine-derived poliovirus type 2 (VDPV2) outbreaks were recorded in Syria, Pakistan, Nigeria and the Democratic Republic of Congo. Priorities in the management of polio for the next six months are surveillance, halting transmission and containment.

M. Malhame described Gavi's progress in three strategic priorities from 2016 to 2020. The first is to support governments in evaluating vaccine introduction and forecasting. The Total Systems Effectiveness sustainability initiative started in 2017 to assist countries to assess future demand, understand trade-offs and make decisions for delivery of best overall value and coverage in varied settings. The second is to support innovations to meet programmatic needs, improving coverage and equity. The third is to actively build industry engagement, by publishing supply and procurement roadmaps for each product and sharing both budget-limited and strategic demand-forecasts [9].

E. Torreele reported that Médecins sans Frontières (MSF) administered over 5 million vaccine doses in over 30 countries in 2015. She acknowledged the critical role of DCVMN manufacturers in improving affordability and access. MSF contributed to overcoming intellectual property and registration barriers and challenged high costs of vaccines where they constitute a barrier to access [10,11]. MSF has also been involved in clinical studies in collaboration with DCVMN manufacturers on vaccine thermostability and clinical trials of new products [12].

A procurement and financing discussion was moderated by S. Sobti, from CHAI.[3] S. Rautio commented that UNICEF continues to support countries graduating from Gavi through the Vaccine Procurement Practitioners Exchange Forum, and through Procurement Services. L. Meng described the Chinese centralized procurement system, with an annual USD 300 million budget,

[3] Clinton Health Access Initiative, www.clintonhealthaccess.org

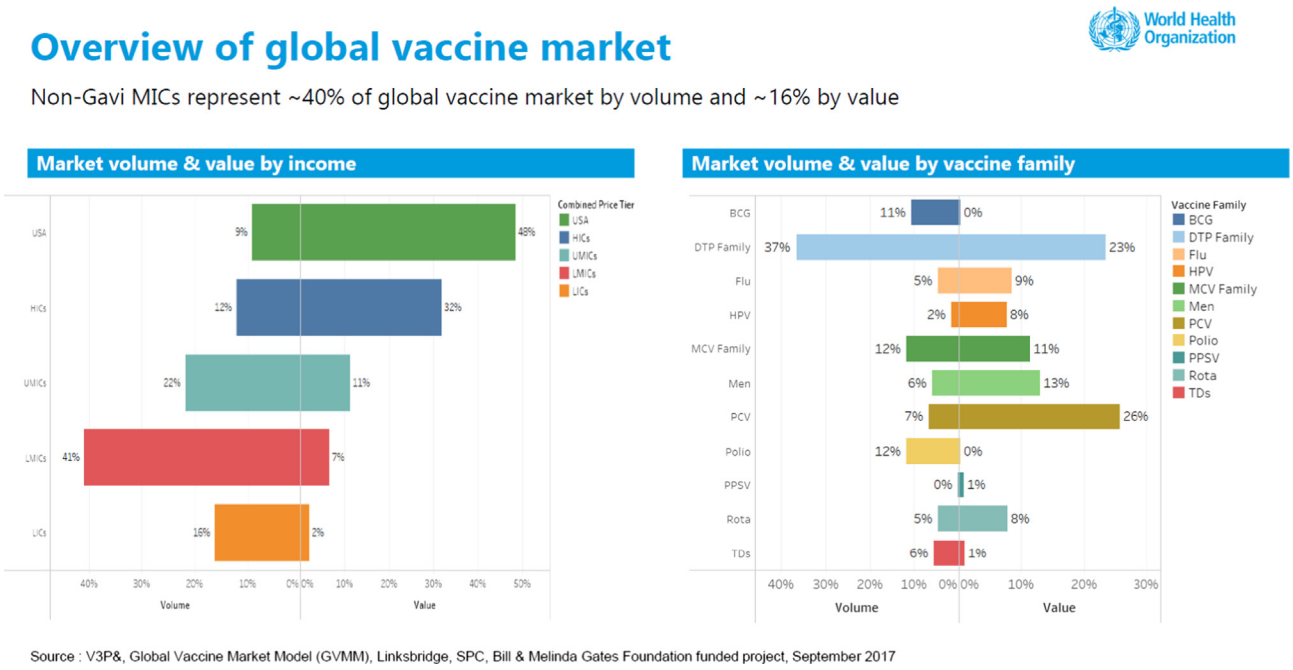

Fig. 2. Overview of global vaccines' markets by income and by vaccine family. Graphic illustration of the proportion of global vaccine market volume and value by countries income groups (left chart) and among 11 vaccine families (right chart). Note that non-Gavi Middle Income Countries represent about 63% of global vaccine market by volume and about 16% by value. USA = United States of America; HICs = high income countries; UMICs = upper middle-income countries; LMICs = low middle-income countries; LICs = low income countries. BCG = Bacillus Calmette–Guérin; DTP = diphtheria-tetanus-pertussis; Flu = influenza; HPV = human papillomavirus; MCV = measles containing vaccines; Men = meningitis; PCV = pneumococcal conjugated vaccines; Polio = poliomyelitis virus; PPSV = pneumococcal polysaccharide vaccine; Rota = rotavirus, TDs = tetanus-diphtheria. Source: V3P&, Global Vaccine Market Model (GVMM), Linksbridge, SPC, Bill & Melinda Gates Foundation funded project, September 2017. Courtesy of T. Cernuschi, WHO.

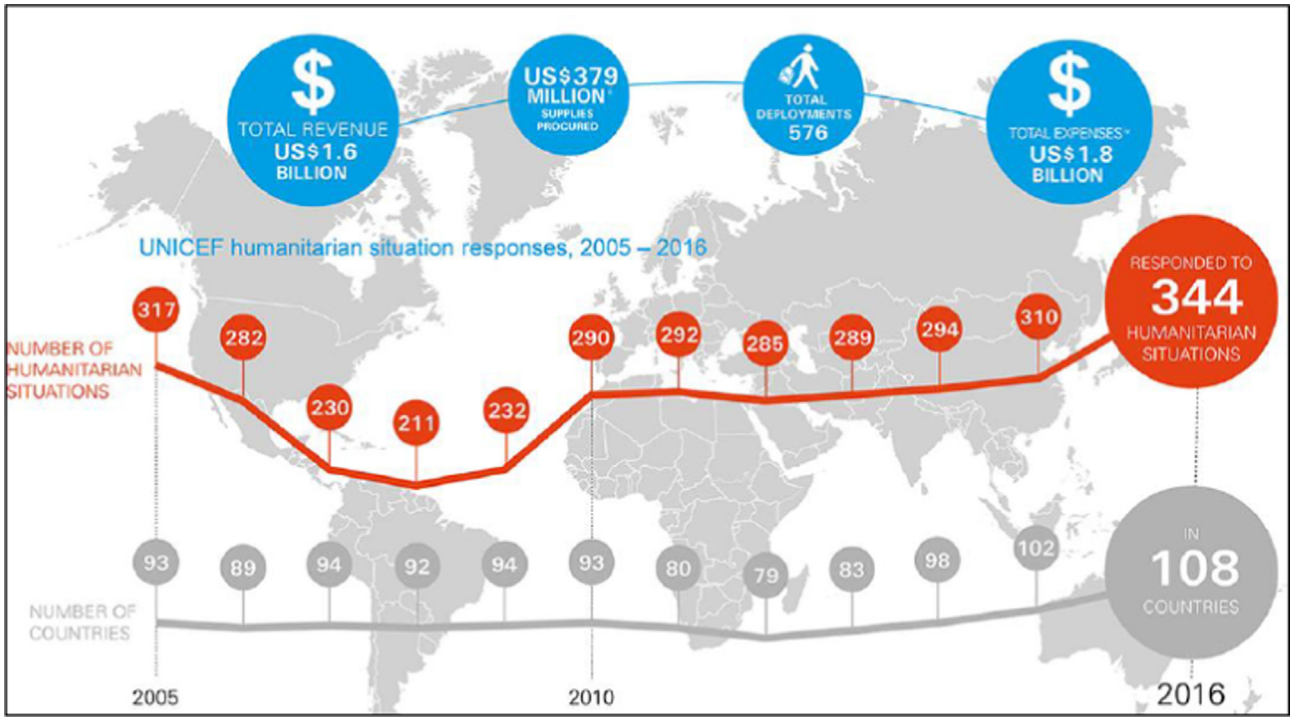

Fig. 3. UNICEF responses to humanitarian situation from 2005 to 2016 showing resources (blue line/blue circles) and number of UNICEF emergency global responses (red line/red circles), and number of countries served (grey line/grey circles) annually, over the last decade. In 2016, 108 country offices responded to 344 humanitarian situations, the most since UNICEF began tracking in 2005. Since 2010, UNICEF has responded to an average of over 300 humanitarian situations in nearly 90 countries each year. Number of country offices in 2016 in responding to emergencies is 37% higher than five years ago (79 in 2012). Courtesy of S. Rautio, UNICEF. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

enabling public and private manufacturers to participate in tenders. S. Bryant, from WHO, elaborated on procurement of vaccines, such as yellow fever and Japanese encephalitis vaccines, for emergency outbreaks. A Joint External Evaluation tool is available to support planning [13]. A. Oswald, from BMGF,[4] recommended balance between affordable vaccines and viable manufacturers investing in large-scale and innovative products, by following each objective separately. There is a need for public organizations to accept higher prices to ensure sustainability. O. Vargas outlined four key principles of the PAHO Revolving Fund for pooled procurement which made immunization in Latin America successful and sustainable: local vaccine legislation, shared goals, solidarity and financial co-responsibility. These provisions resulted in 95% of vaccine costs being supported by national budgets in most Latin American countries.

3. Epidemic and pandemic vaccines

R. Hatchett outlined the gap between late preclinical development and proof-of-concept studies in humans for outbreak vaccines that led to the launch of the Coalition for Epidemic Preparedness Innovation (CEPI) in January 2017. CEPI aims to speed outbreak preparedness and response, ensure market predictability and promote equity of access to vaccines [14]. Targeted times are 16 weeks from antigen identification to clinical trial batch availability, 6 weeks from clinical trial start to demonstration of likely clinical benefit, and 8 weeks from go-ahead to production of 100 million doses. Initial proposals for Middle East Respiratory Syndrome (MERS), Lassa and Nipah virus vaccines are undergoing evaluation.

S. Briand, presented the WHO-strategy for eliminating yellow fever epidemics (EYE) by 2026 [15]. Yellow fever is re-emerging despite availability of an effective vaccine, and now presents a global threat. Forty countries are targeted and 1.4 billion doses of vaccine needed. In 2016 and 2017 there were major urban outbreaks in Africa and South America, and the disease spread to other countries. Population immunity must be increased in high-risk, endemic countries. Successful use of fractional doses in Kinshasa, Democratic Republic of Congo, in 2016, helped alleviate insufficient supply.

J. Kim, IVI, described the MERS 2015 Korean outbreak, the first driven by human-to-human transmission outside of the Middle East [16]. One infected traveler resulted in quarantine of almost 17 000 people, 186 confirmed cases and 38 deaths [17]. MERS outbreaks have been mostly in Saudi Arabia, but global risk of MERS has increased through large-scale travel and migration [18]. There have been 2081 cases with a case fatality rate of 35% (Fig. 4). There are many vaccine candidates, mostly in preclinical testing, but lack of correlates of protection and animal models present challenges. A DNA candidate vaccine has completed preclinical studies and is approved for first-in-human trials [18].

The European Vaccine Initiative (EVI), a product-development partnership represented by O. Leroy, helps control diseases of poverty by building a sustainable vaccine pipeline. EVI's EC-funded Zikavax project, in partnership with Institute Pasteur, Themis and CEA, fast-tracks development of vaccine candidates using a live-attenuated measles vector. The first candidate is in Phase I trial.

A discussion on epidemic and pandemic preparedness was moderated by M. Friede from WHO. O. Leroy highlighted that global leadership and dialogue is needed to establish coordinated strategy and harmonized regulatory requirements. A. Precioso described Butantan's challenges to demonstrate efficacy of its two Zika vaccine candidates in the absence of disease transmission, established tests and agreed clinical endpoints. Human challenge studies may be needed to advance clinical development. M. Zuma, BioManguinhos, noted that high coverage with a full dose in routine immunization against yellow fever provides the best protection for children, while vaccine used at fractional doses can control outbreaks. S. Desai, Zydus-Cadila, discussed the need to build a comprehensive response to Congo-Crimea hemorrhagic fever, including veterinary and human vaccines and post-exposure treatment. R. Hatchett noted that CEPI is developing agreements with companies to support vaccines' manufacturing against diseases with epidemic potential, particularly if there is no routine market for such vaccines. M. Ibna Masud outlined the technology transfer between Incepta, Bangladesh, and IVI on cholera vaccine, with clinical studies in progress.

4. Innovative partnerships

B. Abela-Ridder presented WHO's initiatives to control neglected tropical diseases [19]. Multiple partners pledged support for the control, elimination or eradication of 10 prioritized diseases by 2020. Rabies elimination presents the next major opportunity to prevent 60 000 deaths annually, mostly among children in Africa and South East Asia,[5] aiming zero human deaths from rabies by 2030. Manufacturers are encouraged to prequalify novel rabies products in supporting this initiative.

W. Ampofo spoke about the novel African Vaccine Manufacturing Initiative (AVMI). Africa has 16% of the global population, high population growth and the highest childhood mortality rate, but represents only 5.5% of the global vaccine market. Vaccines are produced at few African facilities, fulfilling only 1% of African vaccine needs. Public health emergencies, such as Ebola, highlighted the regional vulnerability and galvanized support for local manufacturing. AVMI formed in 2010 to advance vaccine manufacture in Africa through advocacy, resource mobilization and capacity-building. An Africa-wide study on manufacturing cost-drivers and procurement in Africa was published. [20]

A. Oswald, BGMF, noted that there are over 100 vaccine manufacturers, which raises strategic questions on how they will compete, and how to balance value and access through partnerships. The current pipeline has many similar vaccines, and prioritizing candidates is challenging. Integration and alignment of purpose and conscientious building of relationships and trust among partners is imperative for sustainable supply.

A discussion on the challenges and benefits of public and private sector collaborations was moderated by G. Rockman of GHIF.[6] M. Makhoana from Biovac announced a product-development partnership with PATH[7] on Group B *Streptococcus* (GBS) vaccine in response to African needs, using a conjugate technology developed with BioNet. A. Gil described Sinergium's partnerships with multinational companies based on a public-private consortium model. Sinergium provided the facility, the multinational provided the product and related technology and local government committed to long-term market tenders. It was successful with influenza, then pneumococcal and, lately, HPV vaccines' supply, in Argentina. K. Ella from Bharat Biotech described their PATH partnership on rotavirus, typhoid and Chikungunya vaccines. P. Khoury from Ology Bioservices discussed a fill-finish service to satisfy bulk manufacturers, small manufacturers and surge capacity needs. B. Abela supported partnerships to sustain access to rabies vaccines. G. Rockman concluded that innovation through complex partnerships requires

[4] Bill and Melinda Gates Foundation, www.gatesfoundation.org

[5] http://global-diseases.healthgrove.com/l/43/Rabies and http://www.dcvmn.org/IMG/pdf/26th_abela.pdf

[6] Global Health Investment Fund, www.ghif.com

[7] Program for Appropriate Technology for Health, www.path.org

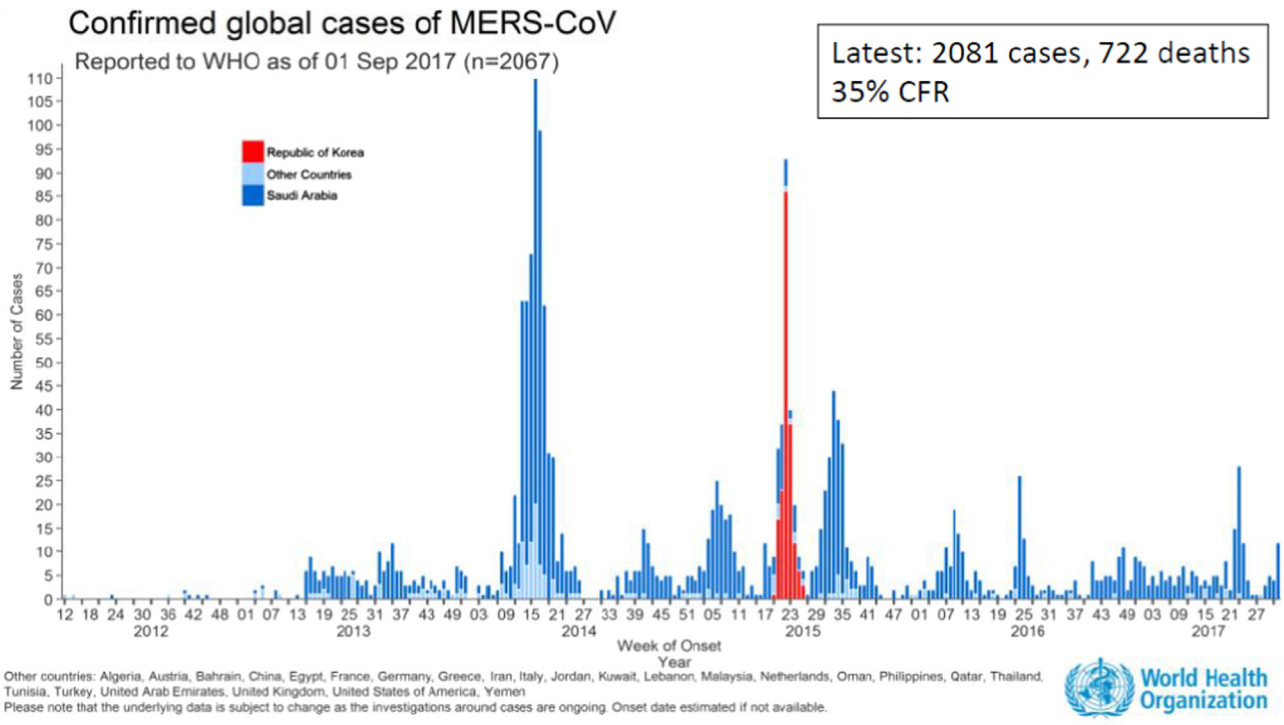

Fig. 4. Confirmed number of cases of MERS globally reported to WHO, since 2012 in Saudi Arabia (dark blue columns), in Republic of Korea (red columns) and other countries (light blue colums). Courtesy of J. Kim, IVI, and WHO. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

sharing of experience and information, and transparency in decision-making.

5. Regulatory convergence initiatives

E. Cooke reviewed the WHO's role in vaccine registration in developing countries, including generating guidance documents such as the Emergency Use and Assessment Listing (EUAL) [21] of pipeline vaccines. Guidance documents are being prepared for nucleic acid, hepatitis E, meningitis B and enterovirus vaccines. To overcome registration delays, avoid duplication of efforts and advance access to vaccines, a collaborative procedure and joint dossier review committees are being implemented.

S. Bhaskaran shared an overview of BMGF's work in supporting the regulatory approval and lifecycle management of vaccines and drugs. Key strategic principles are: Reliance, Re-engineering, and Regionalization. His vision for an efficient, transparent and predictable regulatory pathway for global health products includes moving quickly from manufacturing country, through prequalification, into receiving countries, through adoption of new products.

N. Dellepiane presented a comparative study of dossier format and contents, evaluation procedures and application forms for vaccine registration in different countries [22]. Application forms of eight countries and registration procedures of 134 importing countries were compared, revealing divergence in requirements. Better alignment of the Common Technical Document (CTD) numbering and content, a standardized model-application form and convergence of evaluation procedures, including reliance on WHO prequalification, would improve registration efficiency.

B. Akanmori, WHO, shared his experience in building regulatory capacity through the African Vaccine Regulatory Forum (AVAREF), established by WHO in 2006 in 19 African countries, to overcome regulatory challenges, such as clinical trials, registration and post-licensure surveillance [23].

The experts also discussed the challenges of improving epidemic regulatory preparedness, particularly in countries where Ebola, Zika, MERS, and other outbreaks could surface. Y. Sohn noted that Korea, a PIC/S[8] member country, accelerates approvals through exemption from GMP on-site inspection through agreements and mutual recognition. B. Akanmori mentioned that joint reviews are a successful mechanism to accelerate review of clinical trials and registration applications in Africa [24]. R. Hatchett agreed that well-informed regulators will be better equipped to anticipate needs and evaluate counter-measures. Solutions may include human challenge trials and investigational product stockpiles. D. Dat from Vabiotech added that surrogate efficacy endpoints could be considered for approval of new vaccines, and that, despite harmonized dossiers within ASEAN[9] countries, redundant inspections or supplemental clinical studies still delay registrations. H. Iyer noted that outbreak response time is critical. E. Cooke concluded that communication among regulators is a key to creating solutions to outbreak control. WHO will continue to consider published evidence and proposals to improve the registration of vaccines in developing countries.

6. WHO prequalification updates

C. Rodriguez reviewed the WHO prequalification process, the programmatic suitability for prequalification (PSPQ) of vaccines and the activities following prequalification of a vaccine [25]. Common challenges during prequalification include incomplete dossiers, lack of data (at commercial scale, on cell bank characterization, or lot consistency), inappropriate clinical trial comparator product, non-registration of clinical trials, deficient quality systems, differences between national regulations and deviations

[8] Pharmaceutical Inspection Co-operation Scheme, www.picscheme.org
[9] Association of South East Asia Nations, www.asean.org

from programmatic suitability criteria. Communication, technical assistance and regulatory strategies are in place to reduce these.

She also described the WHO's experience in facilitating access to new Ebola vaccine candidates during the outbreak [23]. Outcomes included expedited review of clinical trials during emergencies, setup of the pre-EUAL process and database [21], strengthening decision-making capacity during emergency responses, and surveillance system improvements.

A. Meek discussed WHO's transition from Product Summary File (PSF) to CTD format, for vaccine prequalification submissions, as CTD use by regulatory agencies has increased. Challenges are anticipated for products licensed in countries not using CTD, and differences in CTD formats. A. Meek also reviewed the WHO position and guidance on bar codes and controlled temperature chain (CTC), referring to the PSPQ2 guideline on programmatic suitability [25]. Label space constraints and cost implications of barcodes are recognized. Presently CTC is intended for campaign and strategic vaccination, not routine use [26]. Stability must be proven, regardless of remaining shelf-life. Additional clinical data is not needed, provided stability tests offer sufficient assurance that vaccines will meet the clinically-tested quality specifications.

7. Innovative solutions for vaccine supply and distribution

D. Zehrung, PATH, reviewed novel primary containers and packaging technologies. Pre-formed plastic vials are being successfully used for oral rotavirus and cholera vaccines. The compact pre-filled auto-disposable Uniject container is used by BioFarma for hepatitis B vaccine. Apiject and Rommelag are developing a blow-fill-seal design for parenteral delivery in a multiple single-dose package configuration. Maropack and a multinational are evaluating the blow-fill-seal technology, to date used only for non-heat sensitive products, for vaccines. Packaging technologies, such as cartridges are being developed by Duoject/PnuVax, for PCV-13 application. Stevanato Group has glass cartridge and ampoule designs. An integrated reconstitution and administration device is being tested for delivery of heat-stable rotavirus vaccine. PATH cost modelling studies confirm that such innovations can reduce the overall costs of vaccine delivery and waste disposal.

A. Kahn provided an update on the WHO CTC, a specific set of conditions allowing vaccine storage and transportation outside of the traditional 2 to 8 °C cold chain for a specified time period [2], applied to vaccines tolerating temperatures of at least 40 °C for at least 3 days. ECTC,[10] refers to vaccines tolerating temperatures above 8 °C for a specified time [26]. Suitability for CTC must be tested, licensed and prequalified. Key tools are Vaccine Vial Monitors (VVMs) at point-of-use and a peak threshold temperature indicator. A CTC working group was established in 2016, at WHO [27].

M. Rush, Temptime,[11] outlined innovations in temperature monitoring. Four established VVM categories are available for vaccines: VVM2, 7, 14 and 30 [28]. A new VVM11 will be commercialized in 2018, and WHO is considering a VVM180. A novel VVM+ is in development for CTC use, combining in a single indicator the cumulative VVM response for temperatures up to 37 °C, and the rapid-response, peak-threshold indicator for high-temperature exposure at 40 °C, 44 °C or 50 °C (Fig. 5). Temptime is also developing a 2D barcode for VVMs with a corresponding reader for both, ideally for use with cellphone application, to improve patient safety and address international anti-counterfeiting, track-and-trace and serialization requirements.

U. Kreysa presented GS1's role in providing global, cross-industry standards for barcoding. WHO's 2015 generic preferred

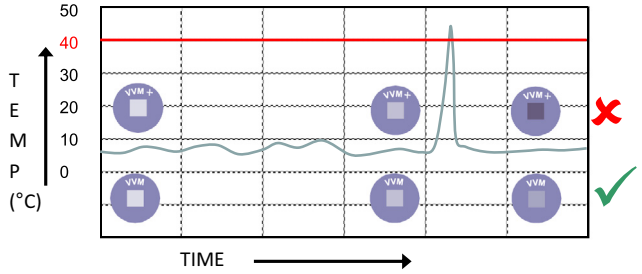

Fig. 5. HEATmarker® VVM and VVM+ color evolution when exposed to a single heat excursion. The HEATmarker VVM+ indicator includes a peak temperature threshold indicator in addition to the VVM in the same device, reacting as a VVM at temperatures up to 37 °C, but reaching the endpoint rapidly after exposure to a defined peak temperature, in this case 40 °C. VVM+ reacts like a VVM up to 37 °C. At 40°, VVM+ reaches the endpoint rapidly to show exposure to critical peak temperature. Courtesy of M. Rush, Temptime.

product profile for vaccines recommends barcodes with GS1[12] standards on all packaging levels used by manufacturers, except primary packaging [29]. While currently voluntary, regulators and buyers may require packaging standards compliance in the future. Pilot projects implementation in developing countries was described [30].

I. Lewis gave an update on UNICEF's barcoding project. Countries' and manufacturers' awareness of CTC has been promoted, and CTC is now a tender-evaluation criterion from 2017. Additional projects support waste and carbon footprint reduction for safe injection equipment. The next tender round will require industry reporting on "green-manufacturing", implementation of weight, volume and local production criteria, and introduction of electronic tendering processes. A vaccine arrival report application has been tested and will be launched globally in 2018.

8. Novel vaccines and technology platforms

S. Kothari, presented an optimized production and purification of typhoid Vi polysaccharide from a clinical isolate from India [31]. Upstream improvements included use of fed-batch culture and optimized media. Downstream improvements optimized diafiltration and replaced precipitation steps with chromatography, resulting in 30–40% higher Vi recovery. Future efforts will focus on reducing product impurities and endotoxins.

L. Liu, from Institute of Medical Biology, Chinese Academy of Medical Sciences, and M. Lundgren, GE Healthcare, presented enterovirus 71 vaccine developed in human diploid cells, or as virus like particles (VLPs) from insect cells, produced in a wave bioreactor, then passed through flow-through chromatography and two binding steps. Flow-through chromatography core beads contain pores which soak up contaminating proteins and small DNA fragments, allowing virus or VLPs to pass through. Wide applicability of core beads for many vaccines was discussed.

P. Tippoo described Biovac's development, with PATH, of a novel vaccine against GBS, a leading cause of sepsis and meningitis in neonates and young infants, and found in a high proportion of pregnant women (10–40%, [32,33]). A pentavalent GBS conjugate vaccine for pregnant women will be based on purified capsular polysaccharide and conjugates for GBS serotypes Ia, Ib, II, III & V.

S. Jadhav, Serum Institute of India, reported on the first thermostable, lyophilized, oral rotavirus vaccine, now available in India [34]. It is a live-attenuated, bovine-human rotavirus re-assortant grown in Vero cells, and includes G1, G2, G3, G4 and G9 serotypes. The lyophilized vaccine is stable at temperatures not higher than 25 °C for 30 months. Three doses showed 66.7% efficacy against

[10] Extended Controlled Temperature Chain
[11] Temptime Corporation, www.temptimecorp.com
[12] GS1, www.gs1.org

Table 1
Existing and desired vaccines, the life cycle and global opportunities for prevention.

BIRTH	CHILDHOOD	ADOLESCENT & ADULT	MATERNAL	OLDER ADULT
Presently Existing Vaccines				
BCG, HepB	D, T, P, HepB, YF, HepA, HIB, PCV, Rotavirus, Rabies, Cholera, MMR, MR, Influenza, HFMD, JE, Poliomyelitis, Meningococcal,	HPV, HEV, Ebola	Influenza	Influenza PPSV, PCV, Zoster, Tetanus
Some Future Desired Vaccines				
RSV	GAS Shigella ETEC	HIV, TB, HSV, Chikungunya Chlamydia Gonorrhoea MERS, SARS, Norovirus, ETEC	RSV GBS Zika	Pneumonia E.Coli S. Aureus Pseudomonas
Further: Better influenza, Pertussis, Polio, and other improved vaccines.				

And. . .Better influenza vaccines, Shigella, ETEC, Norovirus, others
Non-extensive list of vaccines available to date and non-extensive list of desired vaccines for future prevention of known infectious diseases, for vaccination throughout life, from the birth until older adulthood. BCG = Bacille Calmette-Guérin; HepB = hepatitis type B; RSV = respiratory syncytial virus; D = Diphtheria; T = tetanus; P = pertussis; YF = yellow fever; HepA = hepatitis type A; HiB = Haemophilus influenzae type b; PCV = pneumococcal conjugated vaccines; PPSV = pneumococcal polysaccharide vaccines; MR = measles-rubella; MMR = measles-mumps-rubella; HFMD = Hand, foot, and mouth disease; GAS = group A streptococcal; HIV = human immunodeficiency virus; HPV = human papillomavirus; HSV = herpes simplex virus; GBS = group B streptococcus; JE = Japanese encephalitis; MERS = Middle East Respiratory Syndrome; SARS = severe acute respiratory syndrome; ETEC = Enterotoxigenic Escherichia coli. Adapted from, and courtesy of M. Friede, WHO.

severe rotavirus gastroenteritis among infants in Niger [12]. A single-dose, plastic vial presentation is expected to be available by the end of 2018.

The fill-seal technology for inactivated Oral Cholera Vaccine (OCV), described by Y. Baik, Eubiologics, facilitates easy and safe administration of vaccines. Following reformulation of the OCV developed for Vietnam by IVI, the technology and process was optimized at Eubiologics. Clinical studies in 2014 demonstrated non-inferiority [35], the vaccine was approved in January 2015 and WHO prequalification was achieved in December 2015. The fill-seal presentation was validated, approved and prequalified by WHO in August 2017. This presentation reduces package volume by 30% and shipping weight by over 50%, improving storage, transportation and waste management.

M. Lee, from Taiwan, shared the MDCK cell-derived influenza vaccine development using the high-risk pandemic H7N9 strain [36]. Enhanced surveillance for Asian H7N9 viruses in humans and poultry was recommended, as 1557 human cases and 605 deaths were reported to WHO between 2013 and 2017 [37]. A MDCK cell-based influenza H7N9 vaccine candidate, produced at Medigen, underwent clinical trials in Taiwan. Results indicate that inactivated, whole-virus H7N9 vaccine is more immunogenic than VLP, split and subunit antigens [38].

A. Tomar, Cadila Biologicals, presented a new nanoparticle technology platform based on baculovirus and Sf9 cells expressing recombinant, properly folded, functional antigens. The platform has flexibility to manufacture clinical-grade material in 3–4 months, thus is suitable for pandemic or outbreak vaccines. It has been used to produce VLPs for seasonal and pandemic influenza, as well as protein micelles of rabies, Ebola, MERS, Zika and other antigens. A VLP influenza vaccine is now licensed in India, and a recombinant rabies G-protein nanoparticle candidate is in phase III clinical trial.

M. Nahm discussed immunoassay technologies to test vaccines against Streptococcus pneumoniae, a common nasopharyngeal, gram-positive bacterium causing pneumonia, otitis media and meningitis. Polysaccharide vaccines became available in 1987. Polysaccharide conjugated vaccines were licensed in 2000 and 2010 based on immunogenicity data, without efficacy studies, thus reducing costs of new product development. Immunogenicity is measured by the quantitative ELISA or an opsonophagocytosis assay (OPA), measuring protective function [39]. OPA has been multiplexed, allowing accelerated vaccine development through reduced serum requirement, high analytical throughput and availability of robust, standardized procedures [40].

9. Conclusion: The life cycle and global opportunities

In the closing lecture, M. Friede, WHO, considered both novel vaccines and improvements made through advances in production, delivery and administration or protection level and duration. A clear value proposition balancing likely risks and rewards is essential. Needs for additional innovative human vaccines, from birth to old age, were highlighted (Table 1). Vaccination of older adults can prevent illnesses resulting from the age-related decline of immune system function [41–43] as well as consequences of antibiotic resistance. Furthermore, innovative solutions are needed to address the challenge of declining vaccination coverage, affecting 25 countries from 2010 to 2015 [44].

Dr. Friede concluded by appreciating the impact of vaccines on health at all ages, and continual innovation by the vaccine industry. As programmes expand in reach and complexity, innovation and creation of prevention opportunities become more relevant. A major benefit of the DCVMN annual meeting is facilitation of communication between emerging countries' industry and global health organizations.

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Conflict of interest

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