by combining several of these proteins were found to be associated with fewer reactions and were efficacious. Acellular vaccines soon replaced whole cell vaccines in many countries, but because of reduced cost and proven efficacy, whole cell vaccines are still used in most developing countries. There has been a recent increase in reported pertussis cases observed in many countries using the acellular vaccines, especially in young adolescents between 7 to 14 years of age. The reasons for this increase are complex and multifactorial and include greater intensity of surveillance, improved method to diagnose pertussis, changes in the biologic characteristics of the *Bordetella pertussis* organisms, and the types and schedules of pertussis vaccines used for routine vaccination. Current acellular vaccines have been shown to be efficacious in the short term, but in actual use are failing to be effective in controlling pertussis in the long term. Recent data suggest that the acellular vaccines are associated with more rapid waning of immunity, and that priming with whole cell pertussis vaccine is more effective than acellular vaccine in preventing disease. There is a clear need to better understand the differences in the immune responses induced by acellular and whole cell vaccines after both the primary and booster series. Nonhuman primate models are shedding light on the differences in the prevention of disease and transmission with acellular and whole cell vaccines and on the differences in immune responses to both vaccine types. Strategies to improve the current acellular vaccines include; reintroduction of whole cell vaccines into the vaccine series, the addition of new antigens to the currently available acellular vaccines, the use of adjuvants to enhance specific immune responses, and the utility of a new live attenuated intranasal pertussis vaccine

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Time: 10:15-12:15
Room: Auditorium 2

**Dengue vaccine development: An update**

A. Wilder-Smith

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Recent estimates on the burden of DENV infection determined that there are 390 million dengue infections per year, three times the current estimate by the WHO. Since vector control programs have been largely unsuccessful in preventing outbreaks, vaccination seems to be the most viable option for prevention. The development of dengue vaccines has been hampered by the theoretical risk of vaccine-related adverse events such as immune enhancement, and the requirement to induce a long-lasting protective immune response against all four dengue serotypes simultaneously. Other challenges include the lack of an adequate animal model of disease, absence of an immune correlate of protection, and only partially informative immunogenicity assays. Currently, several kinds of dengue vaccines are in development, but only one of these candidates (a chimeric dengue-yellow fever live attenuated vaccine) has reached the stage of phase 3 clinical trials. Live dengue vaccine candidates have been administered to ten thousands of volunteers and were well-tolerated, with minimal short-term safety effects reported in Phase I and Phase II clinical trials. Based on the natural history of dengue, a theoretical possibility of an increased risk of severe dengue as a consequence of vaccination has been hypothesized but not yet observed. Despite good safety and immunogenicity profiles registered, issues such as imbalanced immune responses between serotypes and lack of clinical protective efficacy in the first results of Phase 3 trials have been a major set-back in the development of an urgently needed dengue vaccine.

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**Endgame polio - Vaccine strategies to achieve an end**

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As of December 18, 360 cases of wild type 1 poliomyelitis and 58 cases of paralysis caused by circulating vaccine-derived polioviruses (cVDPV) were reported to WHO in 2013 compared with 223 wild type and 70 cVDPV in calendar year 2012. No wild type 3 cases occurred and all cVDPV cases were attributed to type 2 Sabin derived strains. Among the 3 endemic countries, Nigeria and Afghanistan made substantive progress in controlling WPV1 disease with year-over-year reductions of 58% and 68%, respectively, and further localization of areas experiencing endemic cases. In contrast, Pakistan recorded 75 new cases, an increase of 34% over 2012 due to outbreaks in areas affected by insecurity and poor access to unvaccinated children. New WPV1 outbreaks in the Horn of Africa (203 cases) and Syria (17 cases) were attributed to export of WPV1 viruses from Nigeria and Pakistan, respectively, and 4 cases of paralysis occurred in Cameroon, caused by a WPV1 strain that had been circulating undetected for an estimated 2-3 years. WPV1 viruses related to the Syrian outbreak were detected in environmental surveillance samples beginning in May, 2013 without evidence of paralytic disease in this highly vaccinated country. In response, the Israeli Ministry of Health has re-introduced OPV into the national immunization schedule.

Insecurity, threats to polio vaccination teams, and gaps in supplemental immunization activity (SIA) campaign quality are now major obstacles to eradication which are being addressed by the GPEI in multiple ways including engagement of government and religious leaders and other relevant third parties, and introduction of methods to assess and improve SIA coverage. Ongoing recovery of cVDPV viruses from children with acute flaccid paralysis (AFP) and from environmental surveillance specimens in under immunized areas will mean that cessation of all OPV immunization will need to cease in a globally coordinated manner. The 2013-2018 GPEI Strategic Plan calls for complete control of all wild poliovirus transmission the end of 2014, introduction of one or more IPV doses for routine immunization by Q3 2015 for risk mitigation, and replacement of all trivalent OPV with bivalent type 1 and 3 OPV in Q2 2016. With global certification of eradication by the end of 2018, all OPV vaccines will be discontinued and replaced by IPV.

New tools to assist in achieving and maintaining eradication are under development including new, affordable IPV formulations, genetically stable OPV vaccines derived from current Sabin strains,
and anti-poliovirus drugs to reduce the risk of reintroduction VDPV viruses from chronically infected immunodeficient persons.

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### Novel vaccine strategies to control influenza infections

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The global burden of influenza is substantial. Ample data from high resource settings supports that influenza infection leads to hospitalizations, deaths, excess medication usage, and days missed from work and school on an annual basis. Likewise, there is an increasing recognition of the high influenza burden in low resource countries, although most of our knowledge is limited to the direct effects of influenza illness and less is known about the indirect effects on school or work productivity or the financial consequences.

Influenza is a preventable disease, and advisory bodies throughout the world, including the World Health Organization, recommend influenza vaccine for various age groups and risk groups within the population. In 2013, an unprecedented number of influenza vaccines are available on the worldwide market, including quadrivalent vaccines, live-attenuated vaccines, high dose vaccines, vaccines administered intradermally and vaccines manufactured in cell culture. Many more influenza vaccines are in development, and it is anticipated that the diversity of influenza vaccine choices will continue to increase. Comparative trials are beginning to elucidate the relative benefits of certain vaccines in particular age groups and populations.

This talk will focus on the deployment of particular vaccines and novel strategies to improve influenza prevention programs. The relative advantages and disadvantages of different vaccines and vaccination strategies will be discussed, with a look into the future of influenza vaccine control in various settings.

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### New trends in the treatment of infectious diseases caused by antibiotic resistant bacteria

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Multidrug resistant (MDR) bacteria are a major concern in the worldwide. There remain some useful antibiotics for infectious diseases caused by MDR Gram-positive organisms. On the other hand, treatment of infections caused by MDR Gram-negative bacteria is quite a predicament because the number of effective antibiotics is limited. One of the options is colistin. A lot of articles have reported neurotoxicity or nephrotoxicity with colistin. The injectable colistin does not show enough efficiency for treating pneumonia, because this drug attains low concentrations in the lung. Furthermore, some organisms, including Proteae and *Serratia* spp., show natural resistance for colistin. Colistin is not commercially available in Japan. Another option is tigecycline. This compound shows antibiotic activity against both Gram-negative organisms and Gram-positive organisms. Unfortunately, this drug does not show antibiotic activity against *Pseudomonas aeruginosa*. More therapeutic options are needed. We first constructed a tool for finding combination antibiotics by the modified checker board method. In Japan, the combination of amikacin and aztreonam is most effective combination for MDR *P. aeruginosa* including metallo-beta-lactamase (MBL) producers. Another useful option for MBL producing organisms is the combination of Braian® (EDTA-calcium) and beta-lactams, such as imipenem or ceftazidime. The effectiveness of this combination has been confirmed by in vitro and in vivo experiments using the murine experimental model. Another problem for infectious diseases by Gram-negative organism is endotoxin shock. Polymyxincs can capture the lipopolysaccharides of Gram-negative bacteria. We have evaluated continuously infused low does colistin using microsphere in the murine infection model. Our data suggests that colistin can protect against endotoxin shock. In this presentation, we discuss these novel treatment strategies against infectious diseases caused by MDR Gram-negative organisms.

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