Summer School on Influenza, 2nd edition
Siena (Italy), 16-20 July, 2012

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After a successful first edition in 2011, a second Summer School on Influenza was held in Siena (Italy) from 16 to 20 July 2012. The Summer School was organized and supported by the University of Siena and ISIRV, co-chaired by Emanuele Montomoli, Jackie Katz and John Wood. It was designed for those who were beginning their influenza careers, be it in basic or applied research, government or private sector activities and it was attended by 35 students from Australia, Europe, Egypt, Senegal, India, Philippines, South America and the USA. The students were provided with an excellent introduction to many aspects of influenza ranging from theoretical concepts to basic techniques used in research and surveillance. The scientific program was organized into seven different themes: history, epidemiology and ecology of influenza; prevention and control; influenza virology and pathogenesis; immunity to influenza; influenza vaccines; antivirals and other therapies; regulatory practices and challenges. Two special seminars were focused on vaccination (Rino Rappuoli) and on the 2009 Pandemic (Angus Nicoll). On Monday, 16 July and on Thursday, 19 July some of the students attending the School gave their presentations on their research activities.

After a welcome and introduction on behalf of the University of Siena by Emanuele Montomoli and on behalf of ISIRV by Jackie Katz and John Wood, John Oxford introduced his talk on the medical and social impact of influenza pandemics since 1918 with a discussion on the nature and impact of the influenza A (H1N1) pdm09 virus. The influenza virus which caused the 2009 pandemic and infected approximately 2 billion people in 2009 was a super fit, dominant pandemic virus which appeared to have arisen by classical Darwinian selection. The influenza A (H1N1)pdm09 virus whose HA was similar to that of the 1918 virus was a triple reassortant virus that had emerged from swine. It targets the young, and especially the young who are at risk, including pregnant women whose immune system is somewhat dampened during pregnancy. During the last three waves of the 2009 pandemic, death rates, particularly in children, varied, with a higher rate in ethnic minorities. Oxford also commented on the geographic origin of the 1918 pandemic. Kansas has been identified as the place of origin, but Oxford considers the possibility of an earlier origin in Europe. Two years before the start of the 1918 influenza pandemic, explosive outbreaks of severe pulmonary disease identified at the time as purulent bronchitis occurred in a huge British military camp in Etaples, France and reoccurred in 1917. There is ample photographic evidence of contact between servicemen and fowl and swine, traditional animal hosts of influenza viruses and sources of cross-species viral transmission. Clinical documentation written at the time seemed to imply that the outbreaks of 1916 and 1917, and the 1918 influenza pandemic were essentially the same disease.

Lyn Finelli presented the topic of global influenza epidemiology and surveillance with a definition of influenza as both a virus and a serious respiratory illness with its epidemiological aspects. Influenza is largely a self-limited illness, but severe complications can occur in vulnerable populations such as the very young and the very old. She then spoke about influenza surveillance on a global and national (US) level. The Global Influenza Surveillance Network (GISN) links labs in 106
countries and is essential for vaccine strain selection and as an early warning system for novel influenza virus circulation. In the US, 9 influenza surveillance systems overlap and work together to provide comprehensive national and local information. In addition, epidemiological data gathered through surveillance are needed to identify risk groups and make informed prevention and control recommendations, but this surveillance system is less developed and lacks an international network. Finelli concluded with a discussion of novel influenza virus surveillance. Novel influenza A virus infections are human infections with influenza A virus subtypes that are different from the currently circulating human subtypes (A/H1N1 and A/H3N2). Human infections with novel influenza A viruses that are transmissible person to person may signal the beginning of an influenza pandemic.

Rino Rappuoli discussed the history and development of influenza vaccines focusing on adjuvanted vaccines and their immunogenicity. After briefly describing the influenza virus structure and characteristics, he then discussed the historical development of influenza whole virus, split, subunit, live attenuated, adjuvanted and cell culture vaccines. The adjuvanted vaccine provides heterologous responses to drifted strains. Alum, an adjuvant comprised of aluminum salts, has been in continual use since the 1920’s. MF59, an oil-in-water emulsion adjuvant, was a key innovation; it was the first novel adjuvant in 70 years. Oil-in-water adjuvants have been shown to improve immune response as well as reduce vaccine dose, increasing the number of doses available to meet global demand. The MF59 adjuvanted vaccine can address low vaccine efficacy due to antigenic drift. Memory T cells are induced first, then memory B cells become more abundant following adjuvant priming. As the search for a universal influenza vaccine continues, F16, a truly universal antibody against influenza, recognizes a flat surface on the stem of HA. F16 is the only known antibody found to bind 16 subtypes of the influenza A virus hemagglutinin and is hoped to be useful for a universal influenza virus vaccine.

Angus Nicoll focused his discussion on the problems that arose in the preparation for and response to the 2009 influenza pandemic in Europe. Public health officials and professionals must be able to adapt generic, flexible plans to fit the reality of any specific pandemic, in particular with vaccination strategies and vaccine contracts. They must consider what is already known about influenza pandemics and what is not known so as to act accordingly and prepare for an upcoming pandemic. Countries should prepare for a range of possible pandemics, not just for the worse possible and reasonable case scenario. The ECDC I-MOVE (Influenza – Monitoring Vaccine Effectiveness) project aims at measuring influenza vaccine effectiveness (IVE) in Europe. Its objectives are to identify and pilot test methods to measure seasonal and pandemic IVE in EU and EEA, develop a system to monitor on a routine and real-time basis IVE in EU and EEA, prepare early estimates during the influenza season and have a system ready to assess and monitor IVE in a pandemic. Nicoll concluded that a field vaccine effectiveness system and vaccine safety can be established with the needed infrastructure and some expert capacity.

Emanuele Montomoli gave an overview of influenza vaccine assays used for immunological evaluation. Immunological assays are essential in evaluating candi-
Giovanni Cattoli opened his discussion on animal influenza with an overview of known influenza A subtypes that afflict humans and other animals. All influenza A subtypes are found in avian hosts. Reassortant avian influenza A viruses, containing genes from both American and Eurasian clades, have been reported in wild birds and poultry most likely as a result of intersecting flight patterns leading to contact between infected avian hosts. Scientific evidence suggests that all influenza A virus lineages circulating in animals originally derive from avian influenza viruses. Animal influenza viruses should be capable of finding the appropriate receptors or adapting new receptors (HA-NA molecules) in order to initiate infection, and should replicate and be released in sufficient amount to infect new individuals so as to cross species barriers and to become established in new hosts. Cattoli stressed the importance of controlling the spread of influenza in animals through public health, veterinary and economic initiatives. Animal vaccines and vaccination may help in preserving animal welfare, reducing viral shedding in time and quantity, host susceptibility, viral spread and environmental exposure. Therefore, coordinated interventions are necessary in the animal reservoir to reduce the risk of human infection.

On Tuesday 17 July, Olav Hungnes’ discussion focused on the importance of virological surveillance in accurately finding influenza strains for vaccines so as to be as well prepared when facing an influenza outbreak. It is essential to be able to distinguish influenza from influenza-like illness (ILI) and to confirm influenza disease through accurate diagnosis: Virological surveillance must be organized in order to achieve a representative sampling of circulating viruses and must be capable of rapidly detecting, understanding and responding to emerging changes. On an international level, surveillance should provide timely information about virus trends and evolution, viruses, antigens, reagents and the biannual vaccine and strain process. National networks should cover subtype and lineage identification, antigenic characterization, genetic characterization and antiviral resistance. Since
viruses can evolve rapidly, laboratory methods used for diagnosis and subtyping influenza need to track antigenic, functional and genetic changes that can affect the functionality of tests and protocols. Antigens and genetic characterization of influenza viruses for vaccine strain selection are measured through HI antigenicity and molecular evolution of HA and NA. The high genetic variability of influenza virus strains demonstrates that a flu outbreak can consist of many sub-epidemics. Some apparent patterns, such as spread of epidemic between neighboring countries, can be refuted by virus genotyping evidence.

Jonathan Van Tam discussed influenza disease burden and how it can measure vaccine effectiveness. Backed by several studies, the UK Vaccine Policy in 2012 (the Green Book) defines risk groups who should be offered vaccination: those who are 65 years or over, plus those 6 months and over with chronic diseases, pregnant women, health and social care staff, long-stay residential care homes or other long-stay care facilities, main caregiver of an elderly or disabled person. Death rates and hospital admissions due to influenza examined in various studies are used to recognize and measure disease burden. Influenza vaccination policy is based on disease burden, especially mortality and severe morbidity (hospitalization) and desire to prevent these outcomes. Better evidence of influenza disease burden is needed in health care workers, in acute care settings and in children. The current vaccination policies of several EU countries that do not target children annually, especially those <5 yrs, should be reconsidered given the fact that the influenza virus is a common pathogen among children. Van Tam emphasized the need to monitor vaccine effectiveness and look for improved vaccines.

John Treanor presented two approaches toward vaccine efficacy and effectiveness. In the design-based approach, efficacy is the result obtained from randomized, prospective trials, and effectiveness is the result obtained from observational trials. In the outcome based approach, efficacy relies on results obtained against laboratory confirmed outcomes regardless of trial design and effectiveness is based on results compared against clinical outcomes. Trials using clinical endpoints without laboratory confirmation evaluates both the ability of the vaccine to prevent the infection and the proportion of clinical endpoints specifically due to that infection, which may vary from year to year. These trials enroll a non-representative population and are not feasible in many populations where estimates of efficacy are important. Treanor then examined the effectiveness of antivirals. Amantadine and Rimantadine are orally bioavailable, well tolerated and are effective in prophylaxis and therapy of influenza A in adults. NAI inhibitors have demonstrated improved survival, reduced complications with early therapy, reduced cumulative incidence in seasonal prophylaxis of adults and elders, and reduced secondary attack rates in family prophylaxis in randomized trials. Treanor concluded that there is a clear need for development of better influenza antiviral drugs in the future.

Sylvie Van der Werf analyzed the influenza virus’ structure and replication, focusing on the parts of the influenza viral particle pertinent to influenza vaccine research. Influenza A viruses are enveloped viruses with a segmented negative strand RNA genome. The viral envelope comprises two major glycoproteins, hemagglu-
tinin (HA) and neuraminidase (NA), and the ion channel protein M2. Within the viral particle, the RNA segments are associated in the form of ribonucleoproteins (RNPs) through their association with the nucleoprotein NP and the trimeric polymerase complex made of PB1, the RNA dependent RNA polymerase, PB2, the cap binding protein, and PA, the endonuclease. Viral replication is initiated through attachment of the HA to the viral receptors, sialic acids, and the particle undergoes endocytosis. Low pH in the endosome triggers the conformational change of the HA required for the fusion process which results in the release of the RNPs. These migrate to the nucleus where transcription and replication of the viral RNA segments takes place. Virus RNA replication occurs in two steps: complementary RNAs (cRNAs) of positive polarity are synthesized first and serve as replication intermediates to generate large amounts of progeny virus vRNPs. As for neuraminidase functions, sialidase activity allows the detachment of viral particles, avoids aggregation of viral particles and facilitates transport of the virus through the mucin layer.

Hans Dieter Klenk discussed the determinants of pathogenicity and host range of influenza viruses. The major natural reservoir of influenza A viruses are wild aquatic birds. The viruses occasionally transmit from aquatic birds to other wild and domestic animals and cause infections of varying severity. On rare occasions, they adapt to a new species and form stable host-specific virus lineages. The adaptation of the avian influenza virus to mice is mediated by mutations in the polymerase complex. The influenza virus polymerase is an important determinant of host range, tissue tropism and pathogenicity. Interspecies transmission depends on adaptation of polymerase subunits to importin-α. It has been shown that introduction of mammalian markers enhances pathogenicity for mice. Some of the structural features typical for avian viruses have been preserved in the polymerase of the 2009 pandemic influenza A (H1N1) virus suggesting that this virus has the potential to further adapt to humans. Recent studies found that the expression of sialic acid (SA) receptors in humans varies depending on the region of the respiratory tract. Alpha-2,6-linked SA receptors are abundant in the upper respiratory tract whereas alpha-2,3-linked SA receptors are present mainly in the lower respiratory tract. These limited data led to hypotheses that human and avian viruses may differ in their tissue tropism in humans and these differences in turn may determine transmissibility and pathogenicity in humans.

Wendy Barclay presented the topic of influenza transmission. The influenza virus may be transmitted in humans through direct contact, aerosols and respiratory droplets and contaminated fomites. The virus must escape from the host, survive in the environment and must enter and invade a new host. Environmental factors, such as levels of humidity and temperature, may affect transmission as well as host factors, such as indoor crowding during inclement weather in temperate climate regions. Host susceptibility may be due to fluctuations in immunity; changes in melatonin and vitamin D expression have been implicated. Barclay then spoke about the usefulness of animal models for the study of transmission of the influenza virus. Avian and human influenza viruses bind to different types of sialic acid receptors. Ferrets have the same type of sialic acid cellular receptors as humans. They are
naturally susceptible to human viruses and show similar clinical signs of infection. The influenza virus must replicate to sufficient titers in the respiratory tract, bind to receptors that are abundant in the respiratory tract and survive in the environment, including the respiratory tract, for effective transmission. In assessing risks for pandemic potential of new influenza viruses, H3N2 viruses in North American pigs have reassorted with H1N1pdm09 viruses and acquired a novel M gene. These reassortants are transmissible in ferrets. The small size of the susceptible population may be all that limits this potential pandemic.

Opening Wednesday 18 July’s session, Karl Nicholson started his presentation on influenza disease and management by stating that influenza is just one of more than 150 respiratory viruses. The burden from respiratory viruses other than influenza far exceeds that of influenza. Nicholson then examined several studies on seasonal rates of influenza and virus shedding. Virus shedding peaks early and correlates with symptoms. It is influenced by age, comorbidities, steroid and antiviral use. In an overview of symptom data from 20 studies of approximately 1200 cases involving seasonal and pandemic influenza since the 1930’s, it was found that there was a similarity of illness during pandemic and interpandemic periods and similar illness in different age groups. There was a wide variation in incidence of symptoms: there was no pathognomonic influenza illness, but a prominence of fever, cough, and coryza plus a tendency for headache, myalgia, sore throat and chills. Influenza complications can affect virtually every body system and mortality in hospitals and nursing homes is typically 5 – 10%. Neuraminidase inhibitors have shown cumulating evidence of beneficial effect of early treatment: there was a shorter duration of virus shedding, and a reduction in hospital admissions and illness severity. Moreover, convalescent plasma treatment has been shown to cut mortality in pandemic 2009 H1N1 influenza.

Jackie Katz gave a detailed overview of the immunology of influenza viruses. Innate immunity serves to block the entry of microbes into host tissue as the first line of defense, eliminate or control microbes that succeed in entering the host tissue, instruct cells of the adaptive immune system (T and B cells). The innate response to primary influenza provides early control, slowing replication, but adaptive immunity ultimately clears the infection and allows recovery. Dendritic cells are central to the initiation and regulation of adaptive immunity. CD4+ T cells recognize epitopes that are found on the majority of influenza virus proteins, while CD8+ T cell effectors mediate lysis of virus infected cells by releasing cytotoxic granules. Subtype cross-reactive responses are comprised of T cell responses and antibody responses to conserved proteins/peptides. Influenza infection induces long-lasting B and T cell immunity, but variant strains may overcome pre-existing neutralizing antibody responses and manage to escape both innate and adaptive (B and T cell) responses. Age-related decline in immunological function affects both innate and adaptive immune response. The number of naïve B and T cells is reduced, and a poor stimulation of T cells lead to reduced antibody responses to vaccination.

Rebecca Cox presented the topic of correlates of protection in relation to influenza vaccine development and treatment. A correlate of protection consists of an
immune response that is responsible for and statistically interrelated with protection. A surrogate of protection is an immune response that substitutes for the true immunological correlate of protection which may be known or not easily measured; it may differ in vaccine type and formulation, age and health status. Vaccination is the principal method of protection; it induces a rapid strong systemic but short lived local antibody response. Live attenuated influenza vaccine (LAIV) has been shown to be effective but lacks a correlate of protection. New generation vaccines should not depend only upon the induction of HA specific antibodies as there is a need for detailed evaluation of humoral and cellular immune response including kinetics of response. Vaccine evaluation should be conducted in all age groups, including pediatric and elderly populations. Multifaceted immune responses may cause correlates to vary with vaccine formulation. Further evaluation of the correlates of protection is necessary for continual improvement of vaccine development and influenza treatment.

Otfried Kistner gave a talk on inactivated influenza vaccines in relation to vaccine development. Inactivated seasonal influenza vaccines have been and are routinely produced in embryonated hens’ eggs for more than 60 years. These vaccines have been shown to be safe and effective in all population groups, but with reduced effectiveness in risk groups. Novel alternative cell culture technologies have been developed or are under development for the production of inactivated influenza vaccines as an alternative to egg vaccine production. The world’s demand for influenza vaccine supply suggest that cell culture vaccines cannot replace egg vaccines in the immediate future: both technologies will be used in parallel. Clinical studies have demonstrated that cell culture vaccines are at least as safe and effective as egg vaccines. The immune correlate of protection of an HI titer >40 established for egg vaccines has also been confirmed for a licensed Vero cell culture vaccine. In order to meet increasing global demand in the event of a pandemic in which entire populations would require vaccination, pharmaceutical and biotechnology companies continue to invest heavily to develop solutions that would efficiently increase pandemic influenza vaccine supply by employing antigen-sparing strategies, using manufacturing facilities modified for pandemic production in order to meet biosafety requirements with more facilities based on various production platforms, and by developing different types of influenza vaccine.

John Treanor discussed LAIV and its effectiveness in combating the disease. Infectivity and immunogenicity of LAIV probably depend on prior exposure and susceptibility to influenza viruses. Seasonal LAIV is most effective in unprimed, immunologically naïve subjects such as young children but is probably less effective in adults than TIV. LAIV is safe and well tolerated in all age groups and in individuals with chronic conditions, although wheezing remains a concern in susceptible recipients. It effectively induces mucosal antibody and T cells. Adjuvants or other supplements may enhance vaccine effectiveness for the elderly. Conventional cold-adapted influenza vaccines (CAIV) are highly immunogenic in susceptible populations; they have higher levels of protection for a potential use of low doses, induce mucosal immunity which might reduce shedding and halt transmission, and provide broader cross protection. Strong antibody responses have not been detected and assay
sensitivity is not clear for LAIV. Lack of clear immune correlates for LAIV makes the assessment of its potential role difficult. Alternative approaches for the development of LAIV may include the deletion of some or all of the NS1 protein, the deletion of the M2 cytoplasmic tail, the replacement of the coding sequence of influenza B HA and NA with those of the influenza A virus, and the use of multiple vectors (adenoviruses, poxviruses, etc.) for the delivery of influenza antigens.

Nathalie Landry presented the topic of plant-made influenza vaccines. Plants may be used for recombinant protein production for vaccines as first described in a 1989 study. Plant vaccines have a complex metabolism and are free of human pathogens. There are two main types of influenza plant vaccines currently in use: Recombinant hemagglutinin and HA-VLPs (virus-like particles). Influenza virus-like particles in plant vaccines use only one viral gene, hemagglutinin, leaving no possibility for viral replication. Plant-made VLP vaccines can stimulate innate immunity because VLPs are the same size and shape of a virus leading to better uptake by AFCs. VLP plant-made vaccines have been shown to be safe and well tolerated in clinical trials. The HA-VLP vaccine induces antibody titers comparable to licensed vaccines for effective immunogenicity. Antibody levels detectable 6 months after administration of plant-made VLP vaccine induces innate immune response and long lasting memory through a multifunctional T-cell response. Landry then concluded by addressing the advantages of plant-made vaccines in production and cost. Plant-made vaccines are produced in smaller, less complex manufacturing facilities requiring low capital investment and fixed costs. Plant vaccine production centers are more accessible to emerging countries due to its simpler infrastructure and organization, and have lower production costs and greater affordability for emerging countries’ markets.

On Thursday 19 July, Anna Teresa Palamara gave a talk on redox-regulated intracellular pathways as new, potential targets for anti-influenza drugs. Alteration in redox regulated metabolic pathways may lead to cell damage and eventual cell death, whereas as redox balance maintains homeostasis and regulation of cell functions necessary for cell proliferation and differentiation, and regulation of immune and inflammatory responses. Influenza viruses induce an intracellular pro-oxidant state by decreasing levels of GSH in infected cells. Rapid decreases in GSH levels produce acute cytopathic effects in epithelial cells. The influenza virus activates MAPK signaling after virus entry into the cells through NADPH-oxidase mediated ROS increase after viral challenge to the cell. Diphenyl-iodonium, an NADPH-ox inhibitor, prevents viral-induced ROS increase and GSH decrease. In a study, Palamara found that Resveratrol inhibits p38 MAPK mediated vRNP thereby inhibiting viral replication. Influenza viruses induce different waves of oxidative stress in the epithelial cells. This oxidative stress seems to be essential for vRNP nuclear export and HA maturation. She concluded her presentation affirming that the modulation of host-cell functions essential for viral replication could create a hostile environment for influenza virus survival, block virus-induced inflammation and affect viral replication regardless of virus type or strain.
David Fedson discussed treating the host response in severe influenza disease. Influenza is a multi-system disease that eventually involves cytokine dysregulation, impaired resolution of inflammation, endothelial dysfunction, alterations in energy metabolism and failure to restore mitochondrial biogenesis. Because only small numbers of influenza patients develop severe disease and die, host factors are overwhelmingly the most important factors that determine outcome. In order to understand different host responses, non-influenza scientists have defined common cell signaling pathways in experimental acute lung injury caused by different viral agents. These pathways include molecular targets that are up-regulated in acute lung injury and multi-organ failure and down-regulated by immunomodulatory agents such as statins, fibrates, glitazones and biguanides. Treating patients with severe influenza with immunomodulatory agents should assist a dysregulated host response back toward a state of self-regulated homeostasis which should improve chances for survival. Sharply focused research is urgently needed to determine whether these and other agents that modify the host response might be used to manage severe seasonal influenza and the next pandemic.

Alan Hay spoke about influenza antivirals in his presentation. While vaccination remains the most effective way of combating influenza, antivirals may complement vaccines when vaccines are less effective. Two principal classes of antivirals have been developed and licensed for use against influenza: amantadine and rimantadine, which block the influx of H+ ions through the M2 proton channel, thereby inhibiting uncoating and release of free ribonucleoproteins (RNPs) into the cytoplasm; and zanamivir and oseltamivir (and more recently peramivir and laninamivir) which are anti-NA antivirals that inhibit cleavage of sialic acid from receptors effectively blocking viral release. The emergence of resistance against amantadine/rimantadine and oseltamivir, together with the emergent 2009 H1N1 pandemic, have highlighted the uses and limitations of the available antivirals against seasonal epidemics and in mitigating the early impact of a pandemic. Structural studies of drug-protein complexes have provided detailed understanding of drug action and the molecular bases of resistance. Knowledge of X-ray crystallographic structures of other potential target virus proteins may, as in the case of anti-NA drugs, facilitate the design and development of novel inhibitors of influenza virus replication, essential to increase our options for combating the disease.

Leonoor Wijnans introduced the topic of regulatory practices and challenges in her talk. Marketing authorization for influenza vaccines results from a positive benefit-risk assessment from regulatory agencies. A vaccine’s benefit-risk relationship is defined by clinical efficacy trials with common research protocols which would include validated, standardized assays and a correct choice of assay that offers a relevant response to predict protection. New influenza vaccines require full characterization of immune response, protective efficacy data against clinical endpoints, correlation to clinical protection, long term protection and cross protective immunity. In order to facilitate the evaluation of influenza vaccines and therefore facilitate the development of new and improved vaccines, collaborative efforts are needed to increase understanding of immune markers, their correlation to protection, and to overcome limitations of existing assays to measure these markers.
Even after regulatory protocols have been effectively carried out, the actual safety assessment of vaccines may occur after licensure when the vaccine is in use with possible unforeseen negative outcomes, hence improved systems for monitoring safety is needed. Wijnans suggests that new vaccines should be evaluated in clinical efficacy trials with common research protocols in relevant risk groups.

Finally, on the last day of the summer school, Alan Shaw presented three main areas in developing novel influenza vaccines: M2e vaccines, HA based vaccines, and live virus approaches. Novel influenza vaccines are currently produced in baculovirus-based, tobacco-based and E-Coli-based substrates. Vaxlnnate’s influenza vaccines employ the M2e x 4 fused to flagellin (M2e vaccines) and the HA globular head fused to flagellin (HA based vaccines) methods. Its vaccines are characterized by genetic fusions of the vaccine antigen and TLR ligand which efficiently stimulate both the innate and adaptive immune systems and mimic natural infection. Conventional adjuvanted vaccines, in which the antigen is immersed in the adjuvant, often have an excessive inflammatory response, whereas in the flagellin-based vaccine, there is minimal inflammatory response. Shaw then went on to discuss vaccine production. E-Coli based manufacturing of influenza vaccines are time and cost efficient and have a higher annual production capacity as compared with vaccines made with eggs, cell culture and baculovirus substrates. In conclusion, new vaccines will have to face long and expensive development programs based on efficacy, while the HA-based vaccines have an advantage of having a correlate of protection (HAI).

John Wood addressed EU licensing requirements of seasonal influenza vaccines and the importance of standardization in his presentation. Influenza vaccines must ensure quality, safety and efficacy, and must provide a risk/benefit assessment that includes possible side effects in order to meet licensing requirements. The potency of the vaccine is tested, and serological clinical trials are performed before any actual licensing may occur. There is inherent lab to lab variability of serological assays currently in use. Standardization of lab protocols and the use of antibody international standards should reduce variability among serological assays. It may be possible to reduce variability even further by adjusting laboratory assay results using consensus titers. Regional networks or laboratories could develop their own serology working standards based on international standards. Constant strain renewal and updates in vaccine technology bring challenges for licensing and vaccine standardization. Safe and effective vaccines are achieved through a combination of WHO, national/regional regulatory authorities, public health authorities and vaccine manufacturers working closely together.

The slides of the Summer School on Influenza lectures are available at the web address http://www3.unisi.it/v0/minisito2.html?fld=7566
The Summer School on Influenza also gave the opportunity to commemorate the life and works of Lars Haaheim, co-chair of the first edition who died suddenly on June 28, 2011, two months before the beginning of the school. Tributes to Lars’ scientific achievements and personal qualities were paid during the course, and thanks to the financial support of the Wellcome Trust (www.wellcome.ac.uk/) and the ISIRV Antiviral Group (www.isirv.org/avg), and seven scholarships were created in his honor (The Lars Haaheim Scholarships), in order to support students from developing countries. ISIRV AVG has financed four Lars Haaheim Scholarships, aiming to cover the travel expenses and accommodations of young participants from Brazil, Egypt, Senegal and the Philippines. We would like to thank once again the ISIRV Antiviral Group and the Wellcome Trust, whose generosity has contributed in making even richer and more international the group of participants of the Summer School on Influenza. Our sponsors have been acknowledged on the homepage of the Summer School on Influenza website (www.unisi.it/epidmol - http://www3.unisi.it/v0/minisito2.html?fld=6923) and on the Summer School booklets provided to all the attendees.

The University of Siena Summer School on Influenza Report was written and prepared by staff writer Mario Cruz Panzica of the University of Siena, and revised and edited by Jackie Katz and John Wood of ISIRV, and by Emanuele Montomoli and Francesca Marzari of the University of Siena.
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