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Editorial Board

Vaccines for Influenza A H1N1 (2009)

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Influenza is generally a mild upper respiratory tract infection. It could result in serious complications in children and the elderly. It generally occurs in cold climate in temperate regions of the world and hence is called seasonal flu. In tropical regions like India, transmission can occur round the year with peaks corresponding to rains. The virus causing seasonal flu is very labile and undergoes fine mutations producing 'drifted' strains. These strains bear resemblances to each other and immunity against one protects against the other. However, when the mutation results in creation of a totally new strain (process called 'shift') the population has no immunity against it, and when this strain acquires capability of human to human transmission large segments of population succumb to the infection. As it travels around the world infecting susceptible populations pandemic results. Vaccines against seasonal flu have been available since middle of 20th century. Every year, depending upon the circulating strains, the composition of the vaccine is fine tuned to be as close to the circulating strains as possible to provide optimum immunity. When a new 'shift' strain of influenza emerges, the vaccine manufacturing companies have to change to production using the new vaccine candidate strains. The manufacturing processes for producing pandemic vaccines are identical to those of seasonal flu.

Declaring spread of Influenza A H1N1(2009) (also called swine flu) a pandemic by the WHO was a signal to the vaccine manufacturers to start preparation for production and evaluation of H1N1 vaccine(s).

Production of Seasonal Flu Vaccine

Killed and live attenuated vaccines are currently available for seasonal flu. Presently, there are three predominant types of inactivated influenza vaccine: whole virus, split and subunit vaccines. Majority of influenza vaccines are produced in embryonated eggs. But vaccines for commercial use are now being also produced using mammalian cell lines (MDCK or Vero) which have the potential to decrease the dependency on eggs. A number of adjuvants have been evaluated for their potential to increase the immunogenicity (like the alum, MF59, ASO3, chitosan,

polyinositol) which have modestly improved vaccine response but often at the expense of increased reactogenicity. The current seasonal flu vaccine is a trivalent preparation containing a representative strain of influenza-A (H1N1), A (H3N2) and influenza type-B decided by the WHO annually on the basis of epidemiologic and antigenic analysis of currently circulating strains. The vaccine contains 15 µg of haemagglutinin antigen of each strain.

Once the vaccine strains are identified, it takes about 25-30 weeks to make vaccine available for commercial use.

Nearly 100 countries in the world use seasonal influenza vaccines with variable vaccine usage.

Upstream Influenza Vaccine Approaches

A number of approaches are being pursued to develop alternative forms of seasonal and pandemic influenza vaccines including:

- DNA vaccines expressing haemagglutinin (HA) and neuraminidase (NA), which are delivered to the epidermis by needle-free ballistic delivery of DNA-coated gold particles (PowderMed, Oxford, UK). Preliminary clinical data suggest that this approach is promising, and since DNA can be rapidly produced, this is attractive for pandemic influenza preparedness. The need, however, for a complex formulation and delivery system does remain a barrier to the widespread use of this technology.
- A technology platform has been developed which physically links a natural component of microbes known as flagellin to vaccine antigens. This is based on a combination of toll-like receptor (TLR) - mediated immune enhancement and recombinant bacterial production of vaccine antigen (VaxInnate, USA). These vaccines would be pure, that require no adjuvants and be produced in *E. coli*, indicating that large doses can be manufactured in a short time frame.
- An approach of using recombinant HA produced by a baculovirus-expression system (Protein Sciences Corporation, CT, USA, Novavax USA); or produced in transiently transfected plants (Microbix, USA) has the potential of giving high and rapid yield of antigen. The influenza virus particles contain the viral RNA segments and an assortment of several viral proteins are needed to produce an influenza virus particle. When only HA, NA and M1 proteins are synthesized in cells, particles are released from cell that look very much like the influenza virus. These are called virus like particles (VLP) because they resemble influenza viruses, but lack the viral genome and many other viral proteins. Vaccines using this platform do not use inactivated or attenuated flu viruses as antigen, but use little proteins shells, grown in either plant or insect cells, that look just like real viruses to the body's immune system but that contain no influenza genetic material. The lack of genetic material also spares the need for the formalin and detergent treatments that conventional antigens undergo to make them non-infectious and in the process compromise on their immongenicity.

A study conducted at the Centre for Disease Control (CDC), Atlanta showed that a Novavax VLP vaccine candidate protected ferrets against the 2009 H1N1 virus.[1]

In early December 2009 Novavax, Inc. reported favourable initial results from the first stage of a two-stage pivotal Phase II study evaluating the safety and immunogenicity of the company's 2009 H1N1 VLP pandemic influenza vaccine. Novavax is conducting this study in collaboration with Avimex Laboratories of Mexico to support registration of the vaccine in Mexico and potentially other countries.

In stage A of this study, 1,000 healthy volunteers aged 18 to 64 years were enrolled to receive two doses of 5 µg, 15 µg or 45 µg of Novavax's 2009 H1N1 pandemic influenza VLP or a placebo to determine the safety and immunogenicity of the vaccine. The Data Safty Monitoring Board (DSMB) reviewed preliminary safety and immunogenicity data 14 days post dose one from a subset of approximately 500 subjects enrolled in this stage of the trial. The vaccine was found to be well tolerated at all the three dose levels and exhibited no systemic side effects in this review period. Local site reactions were mild. In this subset of 500 subjects from stage A, the hemagglutinin inhibition (HAI) antibody titers 14 days post dose one in the 15 and 45 µg arms met the seroconversion and seroprotection criteria recommended by the U.S. and European regulatory authorities. Based on these findings, the DSMB recommended that the study proceed to stage B of testing in which vaccine safety will be evaluated in 3,000 subjects with a 15 µg single dose regimen.

The safety and immunogenicity data from all 1,000 subjects in stage A have been made available in January, 2010.[2]

- Recombinant M2e is the extra-cellular domain of the ion-channel protein M2 (Acambis, Cambridge, USA). This is a highly conserved viral antigen and it is suggested that immunity to this antigen could theoretically protect against all A-strains of the virus and thus provide universal protection.

There are about 25 vaccine manufactures (7 have production capacity of more than 2 million doses per week) which have total production capacity of nearly 875 million doses annually. Ninety per cent of these producers are based in Europe and North America. A large proportion of global population lives outside these regions. In case of a pandemic, population of the whole world would need the pandemic vaccine. To offset this geographical imbalance in vaccine production capacity, the Institute of Vaccine Research (IVR) of the World Health Organization has embarked upon a project to establish influenza vaccine production capacity in developing countries by supplying funds and facilitate technology transfer to eligible developing country producers. Killed (subunit, split or whole virus) and live attenuated influenza vaccine production technologies were eligible for funding. Six companies situated in various developing countries were selected. From India, it was Serum Institute of India Ltd., Pune.

Pandemic Influenza A (H1N1) 2009 Vaccine

Whenever there is a major shift in the antigenic characteristics in the circulating virus, it triggers a pandemic and preparations of making a new vaccine strain starts. It has happened with the current H1N1 pandemic. Using techniques of modern biology candidate vaccine strains are prepared and made available to the manufacturers.

While most manufacturers intend to produce only one formulation of the new influenza-A (H1N1) vaccine, some envisage the simultaneous production of two formulations. Thirty three vaccine formulations were identified, most of them based on whole-virion or split-virion antigen, and 12 products would be adjuvanted (in most cases with aluminium hydroxide or as an oil-in-water emulsion). It is estimated that in a best case scenario a maximum of 95 million doses of the new vaccine would be produced per week corresponding to roughly 5 billion doses/year. Governments of various countries started to place orders with the manufacturing companies. On an average they have committed to 1.0 dose/person, resulting in contracts for 850-900 million doses. In addition, most countries have options of signing additional contracts to vaccinate their entire population with 2 doses (total requirement 1.8 billion doses). In the initial 6 months or so there would be little vaccine available for developing countries or those who have not placed orders for the vaccines.[3]

Initiatives in India to Produce Pandemic H1N1 Vaccine

Bharart Biotech, Panacea Biotec and Serum Institute of India are the three biotech companies which have been given an advance purchase commitment for H1N1 vaccine by the Indian Government. Zydus Cadila is the first Indian company to launch Phase-I clinical trial using egg-based inactivated vaccine. Approval of a similar type of vaccine has also been given to Panacea Biotec and Serum Institute of India. Bharart Biotech has also received an approval to launch a clinical trial for a cell culture based vaccine. The first of the Indian vaccines is likely to hit the market by March/April 2010. In addition, Biological E Ltd. has entered into an agreement with USA's VaxInnate Corporation to license its recombinant H1N1 pandemic flu vaccine based on toll-like receptor technology platform. Cadila Pharmaceuticals proposes to utilize virus-like-particle technology to develop H1N1 vaccine as a joint venture with Novavax Inc. a USA based company. Permission to start clinical trials has also been given to Serum Institute of India for live attenuated influenza virus intranasal vaccines.

Preliminary Results of Influenza A H1N1 (2009) Vaccines Trials

Several established seasonal flu vaccine producing companies started work to produce vaccine against the pandemic H1N1 (2009) strain. These vaccines are produced using classical methods that have been used to produce seasonal flu vaccine *viz.* inactivated vaccines (split viruses grown in egg and whose virion virus grows in mammalian cells) and live vaccines (cold adapted, temperature sensitive and attenuated viruses grown

in eggs). The vaccines being produced are adjuvanted as well as non-adjuvanted.

The USA's Federal Drugs Administration (FDA) and Europe Union's European Medicines Agency have given fast-track approvals to the existing seasonal flu vaccine manufacturing companies based on mock-dossiers and rolling-review mechanisms.

CDC's H1N1 Vaccination Recommendations

Recommended Target Groups

- Pregnant women,
- Household contacts of children who are younger than 6 months of age,
- Healthcare workers and emergency medical services personnel,
- Children and young people between the ages of 6 months and 24 years of age, and
- Non-elderly adults with underlying risk conditions or medical conditions that increase their risk for complications from influenza.

In the event of a vaccine shortage, following priority group consisting of a much smaller numbers should be considered for vaccination:

- Pregnant women,
- Household contacts of children who are younger than 6 months of age,
- Healthcare workers and emergency medical services personnel who have direct patient contact or direct contact with infectious substances,
- Children and young people between the ages of 6 months and 24 years of age, and children 5 to 18 years of age who have underlying risk factors that put them at greater risk for complications of influenza.

Source: Use of influenza A (H1N1) 2009 monovalent vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACP) 2009. MMWR August 21, 2009/ 58 (early release): 1-8.

Clinical trials have been undertaken in various age-groups, using different types of vaccines *viz.* adjuvanted, or unadjuvanted, varying amounts of antigen, alone or in combination with seasonal flu vaacine. Results of some of the trials are discussed. By November 2009, results of two vaccine trials had been published.

A H1N1 monovalent, unadjuvanted, inactivated, split virus vaccine prepared from reassortant vaccine virus NYMC Y-179A derived from A/California/7/2009 (H1N1) virus propogated in embryonated chicken egg was tested in healthy adults between ages 18-64 years in Australia. A total of 240 volunteers were equally divided into two age groups (<50 years and >50 years) and randomized to receive either 15 µg or 30 µg of haemagglutinin antigen by intramuscular injection. Preliminary report indicated that by day 21 after vaccination a single 15 µg dose of unadjuvanted vaccine resulted in titres of 1:40 or more in 96.7% of volunteers.[4]

A split-virus, inactivated candidate vaccine against the 2009 H1N1 virus was evaluated for its safety and immunogenicity in a randomized clinical trial in China[5]. Subjects were between 3 and 77 years of age, stratified into four age groups. The immunization schedule consisted of two vaccinations, 21 days apart. Subjects were injected with placebo or with vaccine, with or without alum adjuvant, at doses of 7.5, 15, or 30 µg. Serological analysis was performed at baseline and on days 21 and 35. A total of 2200 subjects received one dose, and 2103 (95.6%) received the second dose of vaccine or placebo. These data suggest that a single dose of 15 µg of haemagglutinin antigen without alum adjuvant induces a typically protective immune response in the majority of subjects between 12 and 60 years of age. Lesser immune responses were seen after a single dose of vaccine in younger and older subjects.[5]

In another study from China, Xiao-Feng Liang and colleagues[6] recruited nearly 12 700 individuals aged 3-87 years from ten centres, all of them followed the same placebo controlled protocol. The investigators evaluated pandemic vaccines from ten manufacturers in eight formulations: 7.5, 15, and 30 µg haemagglutinin, with or without aluminium hydroxide adjuvant, and adjuvanted whole-virion vaccine containing 5 or 10µg haemagglutinin. Immunogenicity was measured by serological responses as a surrogate for vaccine efficacy. Seroconversion was defined as a fourfold increase in haemagglutination inhibition titre to at least 1:40. By day 21, one dose of the 7.5 µg, non-adjuvant, split-virion formulation induced seroprotection in 97% of adolescents (12 to <18 years), 90% of adults (18-60 years), and 80% of older adults (>60 years). In children (3 to <12 years), the

second dose of the 7.5 µg formulation increased the seroprotection rate from 77 to 98%.

From Hungary, Zoltan Vajo and colleagues[7] reported a phase 2 trial in which they recruited 203 adults (18-60 years of age) and 152 elderly people (>60 years) from two centres. Participants were randomised to receive pandemic vaccine only or both pandemic and seasonal vaccines from one manufacturer simultaneously. The monovalent, inactivated, whole-virion pandemic vaccine was formulated as 6 µg haemagglutinin with aluminium phosphate adjuvant, whereas the seasonal vaccine was the annual trivalent formulation with 15 µg haemagglutinin per strain and no adjuvant. When the pandemic vaccine was given alone, 74% of adults and 61% of the elderly individuals seroconverted after 21-28 days. When given at the same time as seasonal vaccine, the corresponding seroconversion proportions were 77 and 82% respectively. Seroconversion to the three strains of the seasonal vaccine varied between 60 and 71% for adults and between 40 and 53% for elderly individuals. No substantial adverse reactions were associated with simultaneous administration of seasonal and pandemic vaccines.

Eric Plennevaux and colleagues from USA[8] reported the preliminary results of a single dose of a pandemic H1N1 vaccine in two phase 2 placebo controlled trials. The trials included healthy children (6 months to 9 years), adults (18-64 years), and elderly people (≥ 65 years). Vaccine doses ranged between 7.5-30 µg and 7.5-15 µg haemagglutinin for adults and children, respectively. Interim results indicated that 92-97% of adults and 83-92% of the elderly participants seroconverted after one vaccine dose. Lower seroconversion proportions, 44-50% for children aged 6-35 months and 67-75% for the 3-9 year old group, suggested that two doses of vaccine would be needed for children aged under 9 years. These studies build on evidence from other vaccine manufacturers that one dose of pandemic H1N1 vaccine is sufficient for seroconversion in healthy adults.

A study, involving 176 adults, 18 to 50 years of age, tested the monovalent influenza A/California/2009 (H1N1) surface-antigen vaccine, in both MF59-adjuvanted and nonadjuvanted forms.[9] Subjects were randomly assigned to receive two intramuscular injections of vaccine containing 7.5 µg of haemagglutinin on day 0 in each arm or one injection on day 0 and the other on day 7, 14, or 21; or two 3.75-µg doses of MF59-adjuvanted vaccine, or 7.5 or 15 µg of nonadjuvanted vaccine, administered 21 days apart. Antibody responses were measured by means of haemagglutination-inhibition assay and a microneutralization assay on days 0, 14, 21, and 42 after injection of the first dose.

The most frequent local and systemic reactions were pain at the injection site (70%) and muscle aches in 42% of subjects; reactions were more common with the MF59-adjuvanted vaccine than with nonadjuvanted vaccine. Three subjects reported fever, with a temperature of 38°C or higher, after either dose. Antibody titers, expressed as geometric means, were higher at day 21 among subjects who had received one dose of MF59-adjuvanted vaccine than among those who had received one dose of nonadjuvanted vaccine ($P<0.001$ by the microneutralization assay). By day 21, haemagglutination-inhibition antibody titres were seen in 77-96% and microneutralization antibody titers of 1:40 or more were seen in 92 to 100% of subjects receiving MF59-adjuvanted vaccine, and in 63 to 72% and 67 to 76% of those receiving nonadjuvanted vaccine, respectively. By day 42, after two doses of vaccine, haemagglutination-inhibition and microneutralization antibody titers of 1:40 or more were seen in 92 to 100% and 100% of recipients of MF59-adjuvanted vaccine, respectively, and in 74 to 79% and 78 to 83% of recipients of nonadjuvanted vaccine, respectively. The study shows that monovalent 2009 influenza A (H1N1) MF59-adjuvanted vaccine generates antibody responses are likely to be associated with protection after a single dose is administered.

Although these trials cover a wide age range of the healthy population, subgroups who have been more severely affected by pandemic H1N1pregnant women, indigenous people, the morbidly obese, and those with underlying co-morbidities have not been included in trials to date. These are considered priority groups for vaccination in many countries, and post-marketing surveillance should include vaccine-effectiveness studies in these groups.

Adverse Reactions/ Safety

Inactivated vaccine

The risks from inactivated 2009 H1N1 vaccine are similar to those from seasonal inactivated flu vaccine:

Mild problems

Soreness, redness, tenderness, or swelling where the shot was given; fainting (mainly adolescents); headache, muscle aches; fever; nausea. If these problems occur, they usually begin soon after the shot and last 1-2 days.

Severe problems

Life-threatening allergic reactions to vaccines are very rare. If they do occur, it is usually within a few minutes to a few hours after the shot. In 1976, an earlier type of swine flu vaccine was associated with cases of Guillain-Barré Syndrome.

Fear of Guillain-Barré Syndrome

In 1976, an H1 influenza virus of swine origin infected soldiers at Fort Dix, New Jersey, and one soldier died.[10] The concern then was that a new pandemic was brewing. A vaccine was developed over the summer months, with clinical trials used to determine the amount and number of doses. Two doses of the vaccine were necessary for persons under the age of 25 years, but older persons had been primed, through natural infection with viruses circulating in the previous H1 era (1918 through 1957) and needed only a single dose to stimulate antibodies against the virus. The government recommended nationwide vaccination, which was performed in more than 40 million people. Unexpectedly, Guillain-Barré syndrome developed in approximately 1 in 100,000 vaccinated persons - a rate 5 to 10 times the background rate. The cause is believed to have been cross-reacting antibodies against peripheral-nerve antigen that may develop after vaccination with the H1 influenza virus of swine origin. The virus did not reappear, and vaccinations were halted. Whether the H1N1 (2009) antigen will cause adverse events if used in a vaccine is not known. The spread of the current H1N1 (2009) is far beyond that of the 1976 event.

Live attenuated influenza virus vaccines

The risks from 2009 H1N1 LAIV are expected to be similar to those from seasonal LAIV:

Mild problems

Some children and adolescents 2-17 years of age have reported mild reactions, including running nose, nasal congestion or cough; fever; headache and muscle aches; wheezing; abdominal pain or occasional vomiting or diarrhoea.

Xiao-Feng Liang and colleagues[6] reported ten randomized trials in which they also looked at safety in individuals aged 3-87 years who received two doses of one of three different H1N1 vaccine formulations. The observed safety profile by antigen content indicated a higher local reactogenicity of alum-adjuvanted split virion formulations compared with non-adjuvanted split-virion formulations (point estimates have non overlapping 95% CIs). The frequency of systemic reactions by antigen content was similar across all groups. With increasing amount of antigen (7.5-30 µg) an increased number of adverse events were reported.

Conversely, with increasing age there were fewer adverse events. The reporting rate for adverse events in individuals who received the 7.5 µg non-adjuvanted split-virion vaccine was lower than in the placebo group (10.3% vs 15.8%). Second doses were administered 3 weeks apart. A lower proportion of adverse reactions were recorded after the second dose of the unadjuvanted split-virion formulation.

Since September 2009, 27 million doses of non-adjuvanted vaccines formulated with 15 µg of antigen have been administered in China.[11] In post-marketing surveillance, the safety profile remains qualitatively consistent with the observations during the trials. Quantitatively, the reporting rate has been lower. Under clinical trial conditions, adverse events were reported by 20.9% of individuals, whereas the reporting rate through the passive surveillance system used during the mass campaign was ten reports per 100 000 vaccine doses administered.

As of December 3, 2009 WHO estimated that more than 100 million doses of pandemic H1N1 vaccines have been administered to health-care workers, people in high-risk priority groups, and the general population since late September, 2009. An independent WHO advisory body, the Global Advisory Committee on Vaccine Safety, convened on December 3-4, concluded that no unexpected safety concerns have been identified for any of the pandemic H1N1 vaccines used in population-level immunization programmes thus far.[12] However, the Committee also cautioned that the countries are at a relatively early stage of the immunization roll-out, and that ongoing safety monitoring and evaluation is needed and outcomes should be rapidly reported. These studies should be complemented by population-level studies on vaccine effectiveness.

Regulators have evaluated the side-effects of pandemic H1N1 vaccines identified through clinical trials and compared the results with the pre-existing and extensive safety database for human influenza vaccines.[13] This work included the 11 years of experience European regulators have with the wide scale use of an oil-in-water (MF-59) adjuvanted vaccine, and several thousands of volunteers who have received another oil-in-water (ASO3) adjuvanted vaccine in clinical trials. In the totality of this information, the conclusion has been that the side-effects observed for the pandemic H1N1 vaccines in clinical trials lie within the expected safety profile for common events with influenza vaccines. Without exception, all products have been registered, meaning that the benefit-risk evaluation has been convincingly positive. Product labeling for each vaccine contains a summary of expected side-effects identified through the clinical studies.

Conclusions

Though there are several measures which aim at prevention of influenza, like wearing of mask, closing the schools, enforcing social distancing, *etc.*, none have been shown to be of clear value. None have been evaluated in the inter-pandemic period, as vaccines and anti virals have been usually available. Thus use of vaccine alone is the best prevention strategy.

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This write-up contributed by Dr. Lalit Kant, Scientist G and Head, Division of Epidemiology and Communicable Diseases, ICMR Headquarters, New Delhi, has been adapted from the Ranbaxy Science Foundation's Round Table Conference Proceedings, Series 23 "Pandemic Influenza Update."

ICMR NEWS

The following meetings of various technical committees/groups of ICMR were held:

Meetings of Task Forces (TFs)/Project Review Committees (PRCs) held during December 2009

TF on Nanomedicine	December 3, 2009
PRC on Malaria, Filaria & Leishmaniasis	December 8, 2009
PRC on Cardiovascular Diseases	December 8, 2009
PRC on Neurology	December 11, 2009
Investigators meeting of the TF on Understanding HIV-Malaria Interaction in Malaria Endemic Region	December 16, 2009
PRC on Otorhinolaryngology	December 17, 2009
PRC on Oncology	December 17-18, 2009
PRC on HIV/AIDS	December 18, 2009
TF on Breast Cancer	December 23, 2009
TF on Diabetes Cohort Study	December 24, 2009

Meetings of Expert Groups (EGs)/Technical Advisory Groups (TAGs)/and other Meetings held during December 2009

Meeting of Leprosy Mission	December 5, 2009
Meeting of Directors of ICMR Institutes/Centres for Data Repository and Business Intelligence	December 8, 2009
EG on Epidemiology of Musculoskeletal conditions in India	December 16, 2009
TAG of Immunization Sub-committee on Rotavirus	December 17, 2009
Indo-US Meeting on Indoor Air Pollution and Health	December 21, 2009
EG of Task Force on Pharmacogenomics	December 22, 2009

Participation of ICMR Scientists in Scientific Events

Dr. P. Vijayachari, Director, Regional Medical Research Centre, Port Blair, participated in the WHO Leptospirosis Burden Epidemiology Reference Group Meeting, held at Geneva (December 2-4, 2009).

Dr. V.A. Arankalle, Scientist F, National Institute of Virology, Pune, participated in the Global Vaccine Research Forum and Parallel Satellite Workshop, at Bomako (December 6-9, 2009).

Dr. Pradeep Das, Director and Dr. P.K. Sinha, Scientist E, Rajendra Memorial Research Institute of Medical Sciences, Patna, participated in the Meeting of the Regional Technical Advisory Group on Elimination of Kala-azar, at Dhaka (December 8-11, 2009).

Dr. Vinod Joshi, Scientist F, Desert Medicine Research Centre, Jodhpur, participated in the Duke-Nus Emerging Infectious Diseases Inauguration Symposium and IV Asian Dengue Research Networking Meeting, at Singapore (December 8-11, 2009).

Dr. V. Kumaraswamy, Scientist F and Officer-in-Charge, Tuberculosis Research Centre, Chennai, participated in the Technical Evaluation Reference Group (TERG) Working Group Meeting, at Geneva (December 9-11, 2009).

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