



Influenza

INFORMATION AND NEWS ON INFLUENZA

EDITORIAL

Since its establishment about 10 years ago, ESWI has put a lot of effort into achieving its principle mission of reducing the impact of influenza in Europe. Its activities have focused on stimulating scientific research and on organising meetings which bring together scientists, healthcare workers, policymakers and representatives of the pharmaceutical industry. This has resulted in their giving more attention to the impact of both epidemic and pandemic influenza and to measures for controlling the disease. They also made major contributions to meetings organised under the auspices of the World Health Organization (WHO), resulting in policy documents about pandemic and inter-pandemic influenza preparedness and a European meeting on pandemic preparedness.

In its tradition of organising scientific and policy meetings, ESWI brings the first European influenza meeting to Malta in October this year. This promises to be a great success. Many scientists have expressed an interest in attending and a challenging programme is emerging.

It is important to keep influenza in the spotlight in a decade where so much is happening in the field. On the one hand we are confronted with a persistent pandemic threat, illustrated by the 1997 and subsequent H5 'chicken flu' episodes in Hong Kong and newly emerging 'drift' and reassortant influenza viruses. On the other hand, scientific and technological

developments have led to new generations of antivirals (the neuraminidase inhibitors), vaccines and vaccine production technologies, and diagnostic tools.

All of these developments in an expanding and culturally changing Europe that is increasingly confronted with new health problems mean ESWI needs to reconsider its strategic plan. Besides being aware of the impact of the disease on current and future target groups, we need optimal implementation of new possibilities for controlling the disease at all levels: surveillance, vaccination, and antivirals. To this end ESWI needs to exploit strategic alliances and communication with scientists, European organisations, policy makers, healthcare professionals, pharmaceutical industries and the media who target the general public. This means we must also further expand the group of ESWI members and advisers with expertise in new fields, something that is being actively pursued.

A new strategic plan should not only aim to increase awareness of the impact of influenza and its control, but also present state-of-the-art strategies and tools to combat the disease. Thus ESWI should be more than ever a 'learning' organisation that constantly readjusts its strategy and policy in a dynamic environment, to reduce the impact of influenza in Europe.

A.D.M.E. Osterhaus
Chair, ESWI

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INFLUENZA VACCINE STRAINS FOR THE 2002/2003 NORTHERN HEMISPHERE SEASON

In February 2002, the World Health Organization (WHO) convened the annual consultation on the composition of influenza vaccines for the Northern Hemisphere. This is a summary of the data reviewed and recommendations for the 2002/2003 season [1].

October 2001 – February 2002 influenza activity

Influenza A (H1N1) viruses were associated with outbreaks in many countries in the Northern Hemisphere. Most isolates were antigenically similar to the previous vaccine strain, A/New Caledonia/20/99. H1N2 viruses, which emerged recently and have circulated in many parts of the world, were the result of genetic reassortment between recent human H1N1 and H3N2 viruses.

Influenza A (H3N2) viruses were isolated sporadically in several countries. Most isolates were antigenically similar to A/Moscow/10/99 and the previous vaccine strain, A/Panama/2007/99. Although some isolates were antigenically distinguishable from these strains, there was no

representative variant. Influenza B viruses circulated widely, causing outbreaks and sporadic cases. Many of these viruses were antigenically closely related to B/Sichuan/379/99. However viruses falling within the older B/Victoria/2/87 genetic lineage have spread to an increasing number of countries in Europe, North America and Asia. These viruses were antigenically related to the B/Hong Kong/330/2001 strain.

Vaccine studies

Vaccines containing A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2) and B/Johannesburg/5/99 strains stimulated satisfactory antibody responses to recent influenza A (H1N1), A (H3N2) and B/Sichuan/379/99-like strains. For influenza B viruses related to B/Hong Kong/330/2001, the antibody responses were lower in titre and frequency than responses to the influenza B vaccine strain.

Vaccine composition

Based on this information, the WHO recommended the following influenza strains in

Northern Hemisphere vaccines for use in the 2002/2003 season:

- an A/New Caledonia/20/99 (H1N1)-like strain
- an A/Moscow/10/99 (H3N2)-like strain*
- a B/Hong Kong/330/2001-like strain.

This vaccine composition was accepted for use in the USA and the EU in March 2002.

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* The most widely used vaccine strain is
A/Panama/2007/99

Reference

1. Recommended composition of influenza virus vaccines for use in the 2002–2003 influenza season. *Wkly Epidemiol Rec* 2002; 77: 62–66.

GLOBAL AGENDA ON INFLUENZA

For some time, the World Health Organization (WHO) has had an Influenza Surveillance Network, which has contributed greatly to the understanding of influenza epidemiology and given an effective basis for regularly updating influenza vaccine formulations. However, influenza surveillance and control needs to be even wider and to this end, the WHO has called for a 'Global Agenda on Influenza'.

The Global Agenda will be a compilation of activities important to mobilise public health action, with the aim of reducing morbidity and mortality from annual influenza epidemics and to prepare for the next influenza pandemic. It will give impartial guidance on research and development to all those involved in influenza surveillance, controlling policy development and advocacy and mobilising resources. The WHO received more than 100 proposals to include in a draft Global Agenda and 75 were categorised into the five sections of the draft Global Agenda: surveillance, disease burden, vaccines, preparedness,

other issues. Between November 2001–January 2002, the draft was on the Internet for open review and electronic discussion. The electronic discussion group is now closed but its results and the Draft Global Agenda can still be reviewed at: www.who.int/emc/diseases/flu/globalagenda/home.htm

A WHO Consultation on Global Priorities in Influenza Surveillance and Control will be held in Geneva from 6–7 May, 2002, to finalise the Global Agenda through working group discussions and plenary sessions. The final Global Agenda is likely to contain between 25–40 priority areas/activities which should fall under one of the four main subjects: improving surveillance, assessing burden of disease, accelerating vaccine use, and pandemic preparedness. About 80 participants were invited to the WHO Consultation, from academia, ministries of health and other health policy-makers, national drug licensing and other agencies, donor agencies, representatives of the International Federation of Pharmaceutical

Manufacturers Association and other private sector groups, international organisations, non-governmental organisations and interested groups. It is hoped that a representative from ESWI will also attend.

The WHO also intends to establish a Global Forum on Influenza, which would be an advisory body on emerging problems, priorities and challenges in influenza surveillance, prevention, control and research. It would also facilitate the exchange of information and support tracking, co-ordination and advocacy of activities in the Global Agenda, regularly reviewing its content and direction.

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INFLUENZA VACCINATION AND HIV INFECTION

Different countries have recommended influenza vaccination for HIV-infected patients at different stages of the disease and the vaccinations have been disputed and recommended again. During the past two years, there have been several studies of this problem.

Several questions were raised:

1. Is influenza more dangerous for HIV-infected patients?

There are contradictory results. Some studies say acute influenza is not a risk for progression of HIV disease [1]. However, a retrospective study in a residential facility for people with AIDS in New York compared an influenza-like illness in HIV-infected and HIV non-infected people. Eight out of 38 of the infected persons against 0/15 non-infected were admitted to hospital, evaluated in an emergency room or had an infection lasting 14 or more days [2].

2. Is influenza vaccine efficient in HIV-infected patients?

It seems to be, but at different levels according to the severity of their HIV infection. Vaccination is especially worthwhile in patients with CD4+ T-lymphocyte counts over $100 \times 10^6/L$ although it may not give the same level of protection as in non-infected subjects [3]. In the New York study previously cited, vaccination was as effective in both groups and most effective in HIV-infected people with CD4 cell counts of >100 cells/ μL or HIV type I virus load of $<30,000$ copies/mL [2]. In a randomised double-blind placebo-controlled trial, 49% of placebo subjects against only 29% vaccinated HIV-infected patients reported respiratory symptoms during the season. Ten out of 23 placebo subjects against 0/16 vaccine subjects had laboratory-confirmed symptomatic influenza. There was no effect on plasma HIV-I RNA or CD4+ cell counts [4].

3. Is influenza vaccine dangerous for HIV-patients?

Increase of the viral load after vaccination of HIV patients has been reported. The recent results confirm this trend at different levels. Some investigators found increased viral load in immunised patients who already had a high viral load at the time of vaccination, but not in those with an undetectable virus load. They concluded that influenza vaccination of severely immunocompromised HIV-infected patients who are failing with highly active antiviral therapy (HAART) might be linked to

immunological impairment [5]. However, others have reported that no influenza-infected patients showed increased HIV RNA levels during and after the infection [6]. Giving vitamin A to children infected by HIV before influenza vaccination dampens the increase in the HIV viral load 14 days after immunisation ($p=0.02$) [7]. For others, the increase of these parameters is rare and transient, when antibody response is impaired with CD4 cell counts of <100 mL and plasma RNA levels of $>100,000$ copies/mL [8,9]. This is of course true for patients under HAART [10]. Other studies did not confirm the changes: in a large study on 36,050 HIV-infected people, a Centers for Disease Control and Prevention (CDC) group found no difference in the evolution of CD4 counts in vaccinated and non-vaccinated patients or in the evolution of HIV RNA levels. The conclusion was that influenza vaccination has no negative long-term effects on CD4 counts or HIV RNA levels in HIV-infected patients and no effect on progression to AIDS or death [11]. Another study concluded that immunisation caused no significant changes in CD4+ counts, nor in plasma HIV-I RNA or proviral DNA levels [12,13]. This is also true for a proposed live influenza vaccine [14].

In conclusion, it appears that influenza vaccination should be considered in HIV infected patients.

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FIRST EUROPEAN INFLUENZA CONFERENCE, OCTOBER 2002

The 'Options for the Control of Influenza IV' meeting held in Crete in September 2000 highlighted the huge number of developments in the field of influenza, from basic science to policies and practices. Because of rapid scientific and public health developments and increased interest in this field, ESWI is organising a major influenza meeting in addition to the 'Options' meetings that are held every four years. This meeting will be held between the 'Options IV' and 'Options V' meetings, with subsequent meetings alternating with the 'Options' series.

The 'First European Influenza Conference' will be held from 20–23 October 2002 in St. Julians, Malta. During the meeting, there will be a special event to celebrate ESWI's 10th anniversary. There has already been

great interest in this meeting with a large number of pre-registrations.

We are very pleased that Dr K. Stöhr from the World Health Organization (WHO) has agreed to give the opening lecture. With this, the WHO and ESWI show their mutual commitment to the fight against influenza. Because of the complex, global issues surrounding interpandemic and pandemic control, there is a need for international partnerships between the key players and stakeholders in this field. This was stressed at a number of recent private and public meetings.

Details and registration forms for the 'First European Influenza Conference', are available on the ESWI website (www.eswi.org). Sponsoring companies will organise a

number of satellite symposia focusing on specific topics.

We would like to thank the advisors and chairpersons of the scientific sessions for their contribution and we trust that the meeting will attract many scientists and public health representatives with an active interest in influenza.

We are grateful for the continued support for ESWI and the generous financial contributions from many sponsoring companies for the 'First European Influenza Conference'.

A.M. Palache

Member of the Organising Committee
First European Influenza Conference

ANIMAL INFLUENZA

Influenza virus types A and B are not only found in humans. Wild (aquatic) birds carry the influenza A virus, transmitting it to domestic birds, pigs, horses, marine mammals and man [1]. Influenza B virus is primarily a human pathogen, although recently it has been found in seals in The Netherlands [2].

In Hong Kong, the avian virus crossed over to the human population and killed six people

In Hong Kong, avian influenza is still a problem, following the outbreak there in 1997 of the highly pathogenic H5N1 influenza that affected poultry farms and live bird markets. During the outbreak, the avian virus crossed over to the human population, killing six people [3]. Since then, surveillance studies for avian influenza viruses have intensified and there have been a number of outbreaks of highly pathogenic influenza in the Hong Kong area. In May 2001, the government was forced to destroy more than 1.2 million birds to limit further spreading of H5N1 influenza virus, an operation that has cost it more than €35 million in compensation. On 1 February 2002, there was another new outbreak caused by an H5N1 influenza virus. To date, 860,000 birds have been destroyed, a large number of poultry farms quarantined and live bird markets closed for brief periods to

prevent a more widespread outbreak. It is important to note that according to local health officials and the renowned leading scientist Professor Shortridge, the H5N1 viruses that caused the recent outbreaks are only distantly related to the 1997 virus, and therefore there is no immediate threat to humans. However, they also warn that the government must act more strongly to control the situation. For more information on these outbreaks visit www.promedmail.org

Approximately 5% of ducks and geese that migrated to Northern Europe in the winter were infected with influenza A virus.

Influenza A viruses are also circulating in wild birds in Europe. Approximately 5% of ducks and geese that migrated to Northern Europe in the winter were infected with influenza A virus. These avian influenza viruses had a broad variety of serological subtypes of haemagglutinin and neuraminidase: in the past three winter seasons, influenza viruses harbouring haemagglutinin subtypes 1–7, 10, 11 and 13 and neuraminidase subtypes 1–8 were found in ducks, geese, gulls and guillemots. The influenza viruses of subtype H5 and H7 found in mallard ducks in The Netherlands were non-pathogenic based on genetic

information and experimental infections of chickens. The Dutch H7 virus appeared to be a close relative of the one that caused outbreaks in poultry farms in Italy in 1999 and 2000. This episode, which started with the circulation of a low pathogenic H7 influenza virus in 1999, developed into a large-scale outbreak of highly pathogenic influenza affecting more than 13 million birds in northern Italy [4]. No other outbreaks of avian influenza have been reported in Europe since then.

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ACTIVITIES OF THE SCIENTIFIC COMMITTEE OF ESWI

Until June 2001, the members of the Scientific Committee of ESWI were: Prof. S. van der Werf (Chairperson), Prof. L. Haaheim, Dr K. Nicholson and Prof. A. Osterhaus. Following the resignations of Prof. L. Haaheim and Dr K. Nicholson, Dr G.A. van Essen was asked to serve on the Scientific Committee. The Scientific Committee would like to thank Prof. L. Haaheim and Dr K. Nicholson for their very valuable contributions.

In line with ESWI's objective of helping to reduce influenza in Europe, the Scientific Committee's purpose is to provide a framework for the initiation, development and evaluation of research projects supported by ESWI.

In 2000 the Scientific Committee selected these research topics:

1. association between laboratory indices of influenza, medical consultations and excess hospital admissions in different age groups
2. relative impact of the use of influenza vaccines and antivirals in the healthy adult population.

The project of Dr T. Heikkinen (Turku University Hospital, Turku, Finland) 'The burden of influenza in children' was selected and awarded €60,000 from ESWI.

In 2001 the Scientific Committee selected these research topics :

1. health care workers immunisation
2. systematic review and economic modelling of influenza vaccines and antivirals
3. general awareness of influenza morbidity and mortality in Europe and barriers to the use of vaccines and antivirals.

Following advertisements in the *Lancet*, *Vaccine* and on the ESWI web site, 11 project outlines were received from seven European countries (Austria, Bulgaria, Czech Republic, Germany, Italy, The Netherlands, United Kingdom), five of them from the United Kingdom.

Most project outlines involved one institution but two involved two and three institutions, respectively. Four proposal outlines were on topic 1, four on topic 2, and six on topic 3. Five were on more than one topic. Two project outlines were judged outside the scope of the topics.

The selection procedure was the same as for the first call proposals. There were detailed discussions of the project outlines by the Scientific Committee based on the following criteria: scientific quality, relevance to the topics and the aims of ESWI, track

record of the research team(s) (based on curriculum vitae and publications), duration of the study, amount of financial support requested.

The committee selected three proposals for full submission. Only two were submitted, which were reviewed by external experts. They were asked to comment on the proposals and rate them for: overall scientific value, potential practical value, originality, adequacy of project design, suitability of methods, feasibility within the proposed timeframe, status of applicant(s) in his/her field.

The Scientific Committee selected the project presented by Dr Amanda Burls (Department of Public Health and Epidemiology, University of Birmingham, UK) on 'The effectiveness and cost-effectiveness of vaccinating low risk groups against influenza in order to reduce transmission to high risk groups: a systematic review of the literature' to be awarded €80,000 from ESWI.

A third call for proposals for 2002 will be launched in April, advertised as previously.

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ESWI WEBSITE

We are online!

For more information about
ESWI please visit our new website at

www.eswi.org

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GUIDELINES

In European countries, influenza immunisation policies used to differ quite a lot [1]. Since the World Health Organization (WHO) guidelines were developed, the differences have vanished for the main risk groups. For children and adults with chronic disorders of the pulmonary and cardiovascular system and diabetes, there is hardly any discussion about the advantages of immunisation [2]. In most European countries the age indication (elderly of 65 years and above) is also settled.

There is still variation among countries for some less frequent indications for vaccination. There is no agreement on pregnancy, renal failure, immunosuppression and long-term aspirin therapy in children, nor for the need to vaccinate healthcare workers. Reimbursement for recommended groups by national or social health insurance is still not settled in all European countries.

Although the vaccination rate is rising in most European countries, there are still considerable differences among them. Moreover it is not clear whether the gross vaccination rate reflects the vaccination rate for the risk groups. There also is no clear-cut relationship between the vaccination rate and the policies for reimbursement. It is possible that the differences are caused by variations in the way guidelines are implemented.

Setting guidelines is one thing, implementing them is something else [3]. From the little research available it is clear that single interventions do not work. Only so called 'shot-gun' methods do. That means that a series of interventions has to be directed at healthcare workers, the general public and the administration.

From the beginning it should be clear which profession is responsible for the whole process. In most countries it is the general practitioner or family physician. Then, all medical specialists should adopt the official policies and the general public should be told of their unanimous point of view. Reimbursement should be dealt with. The transportation of the vaccines to the point of vaccination should be settled to prevent patients going to one place for the vaccine and to another for the injection. Everyone at risk, including healthy over-65s, should receive a personal invitation for the vaccination, with information in comprehensible language. Risk groups should be selected from the electronic medical files, on the basis of (coded) diagnosis or related medication. Finally, walk-in clinics or special vaccination hours could make the organisation smooth and easy for patients as well as general practitioners. Feedback to the general practitioner about the vaccination rate would complete the cycle of quality improvement.

In the light of existing 'guidelines', we plan to evaluate the vaccination rates of certain risk groups in different countries/regions. With others, we intend to monitor the vaccine distribution rate in the main risk patient categories in selected European countries.

We trust this will stimulate health authorities and medical professionals to evaluate their current policy, guidelines and practices for preventing and controlling influenza. This may result in more effective control of the disease.

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NEW ESWI WEBSITE

The ESWI website has recently been redesigned, using the most modern technology. We invite you all to have a look at www.eswi.org

The project began in August 2001 with the aim of modernising the existing site and creating a site dedicated to the upcoming First European Influenza Conference. The project involved the ESWI board and management, web designers and technicians, and an automation consultant. The result is an easy-to-maintain site based on cold fusion technologies with a content management system on top, which focuses on the important topics in influenza.

The following information can be found on the web site: general information about ESWI (including the member list and the annual report), past and present activities and projects of ESWI, forthcoming events on influenza, news, interesting links, an influenza bibliography and the bulletin archive. We are also developing a section with frequently asked questions. You can also contact ESWI through the website.

The site specially dedicated to the upcoming First European Influenza Conference includes a programme and forms for registration and submission of abstracts.

A follow-up project has just begun. The goal is to keep the web site up-to-date. ESWI will establish an 'internet' editorial board with a webmaster/content manager, so that we can respond quickly to new developments in influenza, and make the information available for everyone who is interested. This means that the site is continually changing, so do visit us regularly on www.eswi.org

J. Velzing

*JaDes
Rotterdam, The Netherlands*

INFLUENZA VIRUS: A BIOTERRORIST WEAPON?

The events of September 11th in the USA, followed by the anthrax-letter threats, has not only changed our perception of the risk of bioterrorism (BT) but has boosted general concern about emerging infectious diseases. In the USA this has led to additional billions of dollars of structural funding. Although it is difficult to give a realistic list of the most likely BT agents, most of the circulating 'top ten' lists include highly pathogenic influenza viruses, with or

Highly pathogenic influenza viruses are amongst bioterrorism agents.

without pandemic potential. The pandemic potential of influenza viruses is largely related to individual epidemiological and pathogenic properties. At one end of the spectrum are the annually circulating influenza A and B viruses, responsible for winter epidemics in moderate climates. These are not particularly BT agents, as they do not differ significantly from the circulating strains, which depend on immunity in the exposed population to cause respiratory disease.

At the other end of the spectrum are influenza A viruses with a pronounced pandemic potential, like 'Spanish flu' which cost more than 20 million lives world-wide at the end of the First

World War. These viruses are not readily available and considerable technical skills and facilities would be needed to construct and produce them for BT. Just a handful of laboratories in the world would be capable of this. Furthermore, these viruses cannot realistically be targeted at well-defined groups of people without massive vaccination campaigns to protect peer populations of potential aggressors.

Somewhere between these two extremes are viruses like 'chicken flu' – the influenza A/H5N1 virus – that killed six of 18 infected patients in Hong Kong in 1997. Mass slaughter of all domestic fowl at the Hong Kong marketplaces abruptly interrupted the occurrence of human cases. This confirmed that the virus did not readily spread amongst humans. The high case-fatality rate (33%), the limited human-to-human spread, and the simple technology needed to produce large quantities of this virus in embryo chicken eggs make it, and similar viruses, realistic

Deliberate aerogenic spread in crowded target populations would lead to a self-limiting disaster with many deaths.

candidates for BT. Deliberate aerogenic spread in crowded target populations would lead to a self-limiting disaster

with many deaths. Humans could also be exposed to it through deliberate infection of domestic chickens, with all its public health and veterinary consequences.

Apart from these direct life-threatening effects, an unintended but even more serious consequence could be the re-assortment of the released virus with circulating human influenza A viruses. This would lead to a true pandemic out-

We don't need a bioterror threat to justify a plan to combat it.

break. How well prepared are we to deal with such a scenario? This question becomes crucial when we realise that in the past century, three pandemic influenza outbreaks have killed tens of millions of people. There is no reason to assume that this could not happen now. In fact the recent H5 virus outbreaks amongst chickens in Hong Kong are a clear pandemic warning. We don't need a BT threat to justify a plan to combat it. It is probably more likely that the next influenza pandemic will result from 'natural' inter-species transmission than from a BT attack.

Albert Osterhaus
Chair, ESWI

Rene Snacken
??

CALENDAR OF EVENTS

DATE/VENUE	TITLE	ORGANISER/SECRETARIAT
14–16 May 2002 Prague, Czech Republic	1st International Conference on Immunopotentiators in Modern Vaccines	John Herriot IMV 2002 Secretariat Meetings Management The Barn, Rake Meadow Station Lane, Milford Surrey GU8 5AD UK Tel: +44 1483 427770 Fax: +44 1483 428516
29–31 May 2002 Vilnius, Lithuania	20th Annual Meeting of the European Society of Paediatric Infectious Diseases	European Society of Paediatric Infectious Diseases Visus Plenus Vytenio 9/25 LT-2600 Vilnius Lithuania Tel: +370 2 336138 Fax: +370 2 224124
4–9 June 2002 Opatija, Croatia	3rd World Congress on Vaccines and Immunisation	Edouard Kurstak Infections Control World Organization Faculty of Medicine University of Montreal Montreal Canada H9H 3G4 Fax: +1 514 695 7943
20–24 July 2002 Kentucky, USA	21st Annual Scientific Meeting of the American Society for Virology	Dr S.A. Ghabrial University of Kentucky Lexington KY 40506 USA Tel: +1 859 257 5969 Fax: +1 859 323 1961
27 July–1 Aug 2002 Paris, France	The World of Microbes: 12th International Congress of Virology	ICA a department of JCD Conseil 4 villa d'Orléans 75014 Paris France Tel: +33 1 40 64 20 00 Fax: +33 1 40 64 20 50
24–27 October 2002 Chicago, USA	40th Annual Meeting of the Infectious Disease Society of America	IDSA 432 Columbia Street Unit 11 Cambridge MA 02141 USA Tel: +1 617 621 1398 Fax: +1 617 621 1423

INFLUENZA BULLETIN

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