

Annual report-HPV LabNet-April 08-April 09

Annual Report on

Development of a global HPV laboratory network

(TSA: V31-181-4)

Period:

16 April 2008 to 15 April 2009

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Introduction

A brief introduction of the activities being conducted in your laboratory relating to HPV LabNet.

The activities of the reference lab are considered under the following headings which were part of the 2008 - 2009 Technical Services Agreement with WHO.

In this report, we describe our progress* in each of these Terms of Reference.

Scientific and technical advice

In coordination with WHO, contribute to the development of a global HPV laboratory manual, in collaboration with other HPV experts and HPV network laboratories.

Report: The first draft of the manual was presented at a WHO meeting in January 2008. At the meeting it was decided that worldwide collaborative studies was needed before any HPV assays could be recommended in the WHO manual.

The manual will include chapters on surveillance; nucleic acid amplification technique (NAT) assays and how to assess their performance and make data internationally comparable through the use of international standards; serology assays including EIA and PsV neutralization assays; quality assurance as well as standard operating procedures (SOP); and guidance on some of the specific techniques which had been evaluated through collaborative studies in which HPV LabNet members had participated. It is anticipated that the manual will be finalized in the second half of 2009.

Global Reference Lab (GRL) Sweden participated in the LabNet-wide evaluation of HPV DNA detection and typing tests as well as PsV Neutralisation assays. We also organized and took part of the evaluation of ELISA tests. The 2nd HPV DNA testing and typing Proficiency Panel was organized by us and the data analysis of this effort will be highly useful for an informed text about HPV DNA testing and typing methodology.

Provide scientific advice to the respective WHO regional office or WHO/Headquarters regarding laboratory techniques, including virological and serological detection of HPV infections, for surveillance purposes.

Report: The provision of advice to HQ has been intense with very frequent e-mail exchanges and important provision of advice done at the HPV LabNet meetings, where GRL Sweden made several of the presentations (enclosed).

Collaborate with local and regional public health authorities and research institutions, and other international agencies, who may request advice on monitoring HPV vaccination programs.

Report: We have collaborated with the Swedish Institute for Infectious Disease Control to launch an HPV vaccination registry in Sweden as well as a monitoring system, that uses both condyloma incidence/typing, monitoring of HPV prevalences among teenagers (anonymised testing of Chlamydia screening samples) and systematic typing of cases of HPV-associated diseases.

The PI (Joakim Dillner) has also been expert advisor to the Swedish government on HPV surveillance system design.

Participate in the international collaborative studies to develop HPV laboratory reference reagents for HPV testing, coordinated by NIBSC, disseminating knowledge on, and the use of, HPV international standard reagents to improve the accuracy of DNA and serological measurements.

Report: We have evaluated positive and negative control monoclonal antibodies to be used for characterization of HPV 16 and HPV 18 VLP. The Mabs were sent to us via NIBSC, originally prepared by Neil Christensen, Penn State University.

We have produced 1 mg of HPV 16 and 1 mg of HPV 18 Virus Like Particles (VLP) of serological grade using a mammalian cell expression system., These preparations were sent to NIBSC as candidate VLP to be used in a LabNet ELISA proficiency study.

We have made several lectures about the importance of these standards at national and international conferences.

Conclusion, if any:

We have taken on a substantial part of the task to promote the LabNet and the standardization work.

Quality assurance

In coordination with WHO, contribute to the creation of a HPV quality assurance program for the LabNet by establishing HPV proficiency panels, and assist with analysis of proficiency study results.

Report: We worked out a study plan for doing a HPV DNA quality assurance system by establishing a 2nd HPV DNA proficiency panel together with the WHO HQ, NIBSC and the other members of the LabNet. The study plan was approved by WHO HQ and a contract focused on this task issued. The ToR is enclosed. The panel was manufactured as described and first pre-release testing was done by 2 external laboratories. Following satisfactory results, the second WHO HPV DNA proficiency panel consisting of 43 samples for typing and 2 extraction controls was distributed to 61 laboratories during September and October 2008. A summary report of the 2nd WHO HPV DNA proficiency panel testing is attached.

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We organized a HPV serology testing pre-study according to a study plan developed within the LabNet. The ToR is enclosed. First, a stability test of coated VLPs was performed. HPV 16 coated ELISA plates together with serum and reagents were distributed to all LabNet members. The final report on the HPV 16 pre-study is enclosed.

According to decision taken at the LabNet meeting at WHO HQ in November 2008, the serum samples from the pre-study were tested also by neutralization assay using in-house prepared pseudo-virions. Results of this testing will make it possible to compare the quality of in-house prepared pseudo-virions used within the LabNet. The results of this testing has been submitted to the GRL at CDC, who has coordinated the neutralization study.

At the request of the WHO regional office or WHO/HQ, serve as a resource for preparation, distribution, and/or storage of standard reagents, proficiency panels and cell lines to other laboratories.

Report: See above for storage of the HPV DNA proficiency panel and the bulk stock of plasmids that will enable making more panels (a new one annually is planned).

We plan to send parts of the HPV DNA stock of HPV 6, 11, 31, 33, 45, 52 and 58 to NIBSC to be used as international standards for HPV DNA. Shipment will be done as soon as an adequate MTA is developed and approved by the plasmid owners.

We have started the collection of serum samples to be used as a serology proficiency panel, following an announcement at the WHO website.

Perform confirmatory testing on samples from other laboratories as requested, to ensure that all assays perform at acceptable levels of sensitivity, specificity and reproducibility.

Report: The details on which samples to send was discussed at the meeting in November 2008. We have received about 1000 DNA samples for confirmatory testing from the regional LabNet laboratories. Thailand and Switzerland sent first to us for testing, whereafter we sent the samples further to GRL CDC. India and Japan sent first to GRL CDC, whereafter we received these samples from CDC. Both Australia and Argentina have been responsive and have promised to send samples for confirmatory testing in the near future.

Participate in on site visits to other countries/ provinces as part of the WHO evaluation team, if requested.

Report: This was requested by WHO before addition of the reference laboratory in Argentina, but we could unfortunately not participate as the dates were not suitable.

Conclusion, if any:

We have been progressing with the work regarding HPV DNA testing and typing QA in terms of proficiency panel preparation and spreading awareness of QA principles. We started the work on HPV serology with a pre-study on HPV 16. This work will continue during the next year. The sending of confirmatory samples is an important part of Quality Assurance and has finally started to work.

Training

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Coordinate or participate in WHO training workshops for strengthening the HPV laboratory testing capacity.

Report: This has been requested by WHO for an upcoming training workshop in Thailand in August 2009 and GRL Sweden will participate.

Assure that sufficient trained and qualified personnel and facilities are available to fulfill the tasks related to HPV DNA and antibody laboratory detection.

Report:

Trained personnel available for HPV DNA typing and detection;

Seven qualified persons with HPV DNA testing/Typing certificate (Carina Eklund, Kia Sjölin, Aline Marshall, Christina Gerouda, Anna Söderlund-Strand, Cecilia Wahlström, Lina Thornblad)

Trained personnel available for HPV serology, 2 persons: (Carina Eklund, Helena Faust)

Qualified Supervisory personnel; Joakim Dillner (professor), Ola Forslund (associate professor), Lena Dillner (director)

In conjunction with WHO, provide corrective advice to laboratories within the laboratory network with deficiencies identified by the proficiency studies.

Report: The deficiencies detected and the possible remedies have been extensively discussed at the WHO HPV Lab Net meeting.

Conclusion, if any:

Training has just started and will take a lot more work to be mature. In particular development of proficiency panels, international standards and obtaining supplies of critical reference reagents should be prioritized, as training in the absence of critical reagents or proficiency panels is suboptimal.

Communication

Promote the exchange of information with laboratories at national and regional level and the HPV LabNet.

Report: When WHO HQ opened a Share point for the WHO HPV LabNet, we were transferring all our SOPs to the share point.

We did participated in the 2nd HPV LabNet meeting in Geneva in November 2008.

We have contributed to the WHO HPV LabNet NewsLetter and have distributed this News Letter to all 2240 delegates (from 79 countries) who attended the 25th International Papillomavirus workshop in Malmö, Sweden.

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Provide an annual report to WHO/HQ and respective regional office presenting a critical appreciation of the activities regarding the participation in the global HPV laboratory network.

Report: This is this report. We are also submitting the report to the Regional Office for Europe (att: Galina Lipskaya).

Disseminate relevant information through contributions to a HPV laboratory network quarterly news letters.

Report: We have contributed to the WHO HPV LabNet NewsLetter.

Conclusion, if any:

We need the help of WHO to communicate about the existence of the LabNet as well as inform health authorities, infectious disease control agencies and the scientific community at large about the possibilities of Laboratory Surveillance for promoting effective HPV control by vaccination.

Specific activities conducted by Global Reference Laboratory, Sweden....Please indicate and report by referring to the specific TOR of your laboratory in the TSA.

Prepare an international proficiency panel for HPV DNA and for antibody detection.

For DNA: Completed. See above. For serology: A pre-study for ELISA methodology was performed. A serology proficiency panel will be prepared this year. Control Mabs were tested in collaboration with NIBSC and found to be adequate. HPV 16 and 18 VLP for serology was prepared and sent to NIBSC for characterization, see above.

HPV Laboratory manual- take the lead in coordination and drafting.

At the November 2008 HPV LabNet meeting, it was decided to have GRL CDC to continue leading this work, in order to not accumulate too many important tasks at the same lab. GRL Sweden is contributing to several of the Chapters.

Provide technical services on surveillance & long-term monitoring of vaccination studies.

This is done in close collaborations with the authorities in our country (see above). We aim at designing and trying out a very ambitious program that could serve as a role model for other countries.

Conduct epidemiological studies on HPV prevalence and Vaccination impact monitoring.

This is done in close collaborations with the authorities in our country (see above). We aim at designing and trying out a very ambitious program that could serve as a role model for other countries. The major tools that have been developed so far is an HPV vaccination registry, a high throughput HPV testing and typing system and a joint format for data reporting.

The **Scientific Publications** that have resulted from the work are listed below. We consider it essential to always publish data in the MedLine-indexed scientific literature, as it also greatly contributes to the spreading of information.

Development and quality assurance of improved methods for HPV testing:

Söderlund-Strand, A., Carlson, J. and **Dillner, J.** Modified general primer PCR system for sensitive detection of multiple types of oncogenic Human Papillomavirus. *Journal of Clinical Microbiology*. **47**. 541-546. 2009.

Söderlund-Strand, A., **Dillner, J.**, Carlson, J. High-throughput genotyping of oncogenic human papilloma viruses with MALDI-TOF mass spectrometry. *Clinical Chemistry*. **54**. 86-92. 2008.

Design and piloting of a pilot project with reporting and typing of condyloma acuminata:

Sturegård, E., Johnsson, A., Gustafsson, E. and **Dillner, J.** Condyloma typing important for follow up of HPV vaccination. A condyloma reporting project. *Läkartidningen (Journal of the Swedish Medical Association)*. 105. 3648-3650. 2008.

Using HPV serology for optimizing design of an HPV vaccination program:

Ryding, J., French, K.M., Naucler, P., Barnabas, R.V., Garnett, G.P. and **Dillner, J.** Seroepidemiology as basis for design of a Human Papillomavirus vaccination program. *Vaccine*. **26**. 5263-5268. 2008.

Review articles that specifically discuss the work of the WHO HPV LabNet:

Dillner, L. and **Dillner, J.** International quality assurance of Human Papillomavirus testing. *Central European Journal of Public Health*. **16**. S18-S20. 2008.

Lehtinen, M. and **Dillner, J.** Long-term follow-up of (community randomized) vaccination trials facilitates the implementation of Human Papillomavirus vaccination. *HPV Today*. **14**. 10-11. 2008.

Tegnell, A., **Dillner, J.** and Andrae, B. Introduction of human papillomavirus (HPV) vaccination in Sweden. *Eurosurveillance*. **14**. pii=19119. 2009.

Contributing to International Guidelines on Quality Assurance of HPV DNA testing:

Meijer, C.J., Berkhof, J., Castle, P.E., Hesselink, A.T., Franco, E.L., Ronco, G., Arbyn, M., Bosch, F.X., Cuzick, J., **Dillner, J.**, Heideman, D.A., Snijders, P.J. Guidelines for human Papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *International Journal of Cancer*. **124**. 516-520. 2009.

Arbyn, M., **Dillner, J.**, Schenck, U., Nieminen, P., Weiderpass, E., Da Silva, J.D., Jordan, J., Ronco, G., McGoogan, E., Patnick, J., Sparen, P., Herbert, A. and Bergeron, C. Methods for screening and diagnosis. In: "European guidelines for quality assurance in cervical cancer screening - Second edition". Luxembourg: Office for Official Publications of the European Communities. Chapter 3, 69-152. 2008.

Cuzick, J., Arbyn, M., Sankaranarayanan, R., Tsu, V., Ronco, G., Mayrand, M.H., **Dillner, J.** and Meijer, C.J. Overview of human Papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine*. **26**. Suppl 10. K29-41. 2008.

Review articles specifically discussing HPV vaccination:

Lehtinen, M., French, K.M., **Dillner, J.**, Paavonen, J. and Garnett, G. Sound implementation of human papillomavirus vaccination as a community-randomized trial. *Future medicine. Therapy*. **5**. 289-294. 2008.

Dillner, L., Pagliusi, S., Bray F., Lorincz, A., Kjaer, S.K., Anttila, A., Iversen, O.E., **Dillner, J.**, Lehtinen, M. and Paavonen, J. Strengthening prevention programs to eliminate cervical cancer in Nordic countries. *Acta Obstetrica et Gynecologica Scandinavica*. **87**.489-498. 2008.

Arbyn, M. and **Dillner, J.** HPV vaccination - an overview. Review of current knowledge on HPV vaccination: An appendix to the European guidelines for quality assurance in cervical cancer screening, with addendum. In: "European guidelines for quality assurance in cervical cancer screening - Second edition". Luxembourg: Office for Official Publications of the European Communities. Appendix 2, 267-282. 2008.

Review article specifically discussing the impact HPV vaccination may have on penile cancer:

Bleeker, M.C., Heiderman, D.A., Snijders, P.J., Horenblas, S., **Dillner, J.** and Meijer, C.J. Penile cancer: epidemiology, pathogenesis and prevention. *World Journal of Urology*. Epub ahead of print.

Articles that have used HPV DNA testing and typing (contributing to the stipulated substantial testing volumes that an HPV reference laboratory should have):

Naucler, P., Ryd, W., Törnberg, S., Strand, A., Wadell, G., Elfgrén, K., Rådberg, T., Strander, B., Forslund, O., Hansson, B.G., Hagmar, B., Johansson, B., Rylander, E. and **Dillner, J.** Efficacy of HPV-based primary cervical cancer screening with cytology triage or repeat HPV test. *Journal of the National Cancer Institute*. **101**. 88-99. 2009.

Dillner, J., Rebolj, M., Birembaut, P., Petry, K-U., Szarewski, A., Munk, C., de Sanjose, S., Naucler, P., Lloveras, B., Kjaer, S., Cuzick, J., van Ballegooijen, M., Clavel, C. and Iftner, T. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *British Medical Journal*. 337:a1754. 2008.

Bjerre, P., Silferdal, L., Dillner, L., Hagmar, B., Edvardsson, H., **Dillner, J.** and Andersson-Ellström, A. A randomized trial of basing treatment on HPV and/or cytology results in low grade cervical lesion triage. *American Journal of Obstetrics and Gynecology*. **199**. 24.e1-24.e7. 2008.

Articles that has used HPV serology (contributing to the stipulated substantial testing volumes that an HPV reference laboratory should have) and has validated a new high throughput method for HPV serology:

Dickson, N.P., Ryding, J., van Roode, T., Paul, C., Herbison, P., **Dillner, J.** and Skegg, D.C.G. Male circumcision and serologically determined human papillomavirus infection in a birth cohort. *Cancer Epidemiology, Biomarkers & Prevention*. **18**. 177-183. 2009.

Recommendations to WHO HPV LabNet

Please provide any comments, conclusions on this years progress, make any recommendations to WHO for the next year activities. These will be very helpful for understanding the current status of the subject, identifying the gaps/needs, and planning for the next steps in the whole pipeline.

Points for improvement:

- All member labs should send samples for **confirmatory testing**. This is a very straightforward, simple and clear task that is specified in the ToR and would quickly raise the quality standards of the network. This works now for most laboratories, but the few member labs that do not do it should be encouraged to also do this. The consensus agreed protocol (at the First HPV DNA LabNet Workshop) on exactly which samples should be sent is enclosed. A HQ move – e.g. to make sending samples for confirmatory testing a requirement for funding - would be helpful.

-The **International Standard** for HPV18 antibodies should have progress. We had problems to source this reagent ourselves and asked both the LabNet and the world (through a message at the WHO website) to assist in donating samples that could be used as an HPV18 International Standard. As there was no progress in sourcing this reagent by asking other for help, we have resorted to trying to source the reagent ourselves again. It appears that this will now be possible, but there has been quite some delays in this project.

-We need to collect a supply of **critical reference reagents** for HPV antibody testing. These are too difficult and cumbersome to prepare in every lab. Specifically:

2. Virus-like particles of serological grade. We need to identify someone who can produce high quality VLPs in substantial amounts. The WHO call for VLP donations has indeed resulted in several donations of VLPs that are currently being characterized and the prospects for identifying a stable source of high quality VLPs seem promising today.

3. Pseudoviron stocks for neutralization assays. Same issue as for the virus-like particles. It is well known how to do it- but a producer laboratory is as yet not identified. This has not been high priority so far, but the promising results of the International Collaborative Study on neutralization suggest that maybe this should be prioritized.

-**Communication** needs to be prioritized! Many countries may right now be starting vaccination programs without even thinking about a surveillance program and by the time they realize the need, they have no pre-vaccination baseline. The possibilities of HPV Laboratory surveillance needs to be communicated as efficiently as possible and through the most relevant and authoritative channels. Although the LabNet can help in writing scientific publications that appear in MedLine, by the NewsLetter and by posting material at the LabNet homepage at HQ, more authoritative and professional communication strategies would be required, particularly when it comes to reaching infectious disease control agencies and health policy makers that should be thinking about HPV laboratory surveillance. Active spreading of information via the WHO Regional Offices is suggested.

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There should also be an increase focus on scientific publication from all the reference laboratories.

-Involving National Reference Laboratories.

Many countries (E.g. Germany, France and Scotland) have officially appointed National Reference Laboratories for HPV Surveillance and several of these laboratories have been very eager to join the LabNet. Obviously, if these countries design baseline HPV surveillance strategies that are different from the WHO strategies, it might be difficult for them to change the strategies later in order to adopt to internationally comparable strategies and HPV testing technologies. That the WHO HPV LabNet is “keeping the national reference laboratories out” is just about the only frequently voiced critique against the work of the WHO HPV LabNet that we have encountered. If it is not possible to involve them as members at this stage, involvement as observers is suggested.

Proposed specific activities for the next year

Please propose next year workplan regarding "specific activities" your laboratory will conduct pertain to the mission of HPV LabNet.

This will be subject to discussion/modification and servicing as the basis for the next year TSA.

For any activities have not been implemented against the TORs, please indicate any reasons and further action.

We have structured the proposed tasks in a Table, below:

PROJECT	SUB-PROJECT	What should be done	Time-line
DNA proficiency panel, 3 rd panel	Preparation of panel Annual report-HPV LabNet April 08-April 09	The 3 rd DNA proficiency panel will contain re-cloned characterised HPV 39, and well characterised HPV 68a and ME180 (HPV 68b) isolates. It will also include several DNA extraction controls.	March – July 2009
	Distribution	The panel will be distributed within HPV LabNet in September 2009.	September 2009
	Preparation of report	All laboratories should send the results back within 4 weeks. Report to WHO	November 2009 Dec 2009
SOP for HPV LabNet proficiency study AND for confirmatory testing	Draft Circulation in LabNet Finalization	It's now mature to formalize SOP for conducting the HPV LabNet proficiency study and confirmatory testing as a formal document/practice which shall include principles, panel preparation, evaluation, distribution, study organization, data reporting, analysis, criteria, summary report, feedback to labs, and all critical elements involved in the study. This is to keep consistency of the studies conducted in a standard manner. Submit to WHO as a final version	August September-October Done by Dec 2009
DNA proficiency panel 2 nd panel	Paper	The report to the WHO has been delivered, but the results will also be reported in the format of a scientific paper.	June 2009
Laboratory manual		The laboratory manual should be written during 2009. The global reference laboratory at CDC is responsible for this. All chapters should be sent to Dr Unger Final version approved J. Dillner should draft; Surveillance (together with Unger and Garland) Serology (with Nardelli and Garland) DNA information on 2 nd proficiency study GRL Sweden will provide necessary assistance until the Manual is approved by WHO for publication if needed.	September 2009 July 2009.
International reference sera for HPV 18	Identify a source Testing of serum	To be able to compare serological test results between different laboratories an international reference serum for HPV 18 is developed. Needs to find serum donors. When serum collection has started all sera will be analysed for HPV 16 and 18 antibodies. The same screening of donors will be used to select sera for a serology proficiency panel. In addition sera for the proficiency panel will be donated according to call and characterized by us.	September 2009 September-October 2009
VLP-ELISA	Preparation of VLP Characterization of VLPs	LabNet needs a source VLPs to be able to standardise HPV serology. GRL Sweden has prepared 1 mg HPV 16 and HPV 18 VLP for characterisation by NIBSC and use in the 2 nd phase VLP ELISA study. GRL Sweden will characterize this source and other sources in parallel. IF necessary we will make more mammalian VLPs	August 2009
VLP-ELISA	2 nd phase VLP ELISA study	To ensure that prime HPV serology is established at all LabNet labs, and to gather data to help establish a well accepted "cut-off". -Serum for the proficiency panel to be used should be sent in by all laboratories.	Initiated in May 2009 February 2010

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Confirmatory testing		<p>Will retest samples that have been sent in by LabNet labs. All laboratories should send; all HPV negative cervical cancers, all "HPV X" and 100 random CIN 3 or CxCa.</p> <p>As some regional reference labs sent these samples only recently, testing for 2008 will not be completed until November 2009.</p> <p>The process should be repeated every year for maintaining proficiency in participating laboratories</p>	<p>November 2009</p> <p>Next year completed by June 2010</p>
Joint format for recording data		<p>A standard format for recording data is required for being able to assemble data from many laboratories. GRL Sweden will suggest such a format. Five laboratories withing HPV LabNet that were interested in trying out the format (piloting) were identified at the November 2008 WHO HPV LabNet meeting.</p> <p>Pilot study completed and report written.</p>	<p>August 2009</p> <p>January 2010</p>

Additional tasks:

*Assist WHO and NIBSC in efforts to develop standard supplies of

1. Positive and negative control monoclonal antibodies.
2. Virus-like particles of serological grade.
3. Pseudoviron stocks for neutralization assays.

We will assist with 1) advise and 2) quality control testing of these reagents.

BUDGETARY BREAKDOWN:

Delivery of specimens to LabNet labs and NIBSC. Courier fees. Tubes and boxes: 9000 USD

Equipment (part of minus 80 degrees freezer for maintaining reagents): 7000 USD

Consumables & Critical Reagents (ELISA plates, consumables for making VLPs/pseudovirions; tissue culture reagents for growing cell lines (DNA extraction controls), Qiagen kits for DNA purification, DNA characterization reagents, primers and probes for confirmatory testing): 26 000 USD

Training, administrative overhead: 8000 USD

TOTAL: 50 000 USD

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LIST OF ENCLOSURES

1. Final Report, WHO HPV LabNet HPV DNA typing Proficiency Study
2. Final Report, WHO HPV LabNet HPV16 Serology Pre-Study
3. Call for contribution of human serum samples for proficiency study, published at the WHO website
4. Call for contribution of virus-like particles for serology, published at the WHO website
5. Slides from 5 lectures held at WHO HPV LabNet meeting at WHO HQ in November 2008
6. Selected scientific publications (see list on Page 5-9)

Lund 8/6 2009

Joakim Dillner