

Imiquimod versus podophyllotoxin, with and without human papillomavirus vaccine, for anogenital warts: the HIPvac factorial RCT

Richard Gilson,^{1,2*} Diarmuid Nugent,^{1,2}
Kate Bennett,³ Caroline J Doré,³ Macey L Murray,³
Jade Meadows,³ Lewis J Haddow,^{1,2} Charles Lacey,⁴
Frank Sandmann,^{5,6} Mark Jit,^{5,6} Kate Soldan,⁶
Michelle Tetlow,³ Emilia Caverly,³ Mayura Nathan⁷
and Andrew J Copas^{3,8}

¹University College London Centre for Clinical Research in Infection and Sexual Health, Institute for Global Health, University College London, London, UK

²Mortimer Market Centre, Central and North West London NHS Foundation Trust, London, UK

³Comprehensive Clinical Trials Unit, Institute of Clinical Trials and Methodology, University College London, London, UK

⁴Centre for Immunology and Infection, Hull York Medical School, University of York, York, UK

⁵Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

⁶Statistics, Modelling and Economics Department, Public Health England, London, UK

⁷Homerton Anogenital Neoplasia Service, Homerton University Hospital NHS Foundation Trust, London, UK

⁸Medical Research Council Clinical Trials Unit, Institute of Clinical Trials and Methodology, University College London, London, UK

*Corresponding author r.gilson@ucl.ac.uk

Declared competing interests of authors: Richard Gilson reports grants from the National Institute for Health Research (NIHR) during the conduct of the study. Lewis J Haddow reports grants from the NIHR Health Technology Assessment programme during the conduct of the study, grants from the British HIV Association's Scientific and Research Committee and personal fees from Gilead Sciences, Inc. (London, UK) outside the submitted work.

Published September 2020

DOI: 10.3310/hta24470

Plain English summary

The HIPvac factorial RCT

Health Technology Assessment 2020; Vol. 24: No. 47

DOI: [10.3310/hta24470](https://doi.org/10.3310/hta24470)

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Plain English summary

The HIPvac [Human papillomavirus infection: a randomised controlled trial of Imiquimod cream (5%) versus Podophyllotoxin cream (0.15%), in combination with quadrivalent human papillomavirus or control vaccination in the treatment and prevention of recurrence of anogenital warts] trial compared two commonly used creams to treat genital warts: 0.15% podophyllotoxin cream (Warticon®; GlaxoSmithKlein plc, Brentford, UK) and 5% imiquimod cream (Aldara®; Meda Pharmaceuticals, Takeley, UK). It also investigated whether or not a vaccine used to prevent human papillomavirus infection, quadrivalent human papillomavirus vaccine (Gardasil®, Merck Sharp & Dohme Corp., Merck & Co., Inc., Whitehouse Station, NJ, USA), could help treat warts or prevent them from coming back in patients whose warts had been cleared.

The HIPvac trial was a randomised controlled trial involving 503 patients with warts attending sexual health clinics in England and Wales. The creams and the vaccine were well tolerated; there was some soreness where the cream was applied, but no unexpected side effects.

When deciding which treatment was better, we looked at whether or not the warts had cleared by 16 weeks after starting treatment and, if cleared, whether or not they returned by 48 weeks. We compared the creams against each other, and the addition of vaccine against no vaccine (a placebo injection). Patients were allowed to have cryotherapy (freezing treatment) as well, if the investigator advised this. We also calculated the value for money of each type of treatment.

The two creams were very similar in how well they worked to clear the warts. One difference was that podophyllotoxin cream worked slightly quicker. The number of patients given cryotherapy was about the same for both types of cream. We had expected that recurrence of warts after treatment with imiquimod cream might be less than after treatment with podophyllotoxin cream, but, in fact, the two creams were similar.

Quadrivalent human papillomavirus vaccine did not improve clearance of warts or reduce the chance of recurrence, but the result remains inconclusive. If we had been able to recruit 1000 participants as originally planned, we might have been able to be more certain about whether there was any benefit of vaccination. Further research would be needed to investigate any possible effect.

The two creams offered similar value for money in treating warts. Giving patients the vaccine in addition to the cream is not good value for money at its current list price, given the uncertainty about the benefit it offers.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 11/129/187. The contractual start date was in September 2013. The draft report began editorial review in December 2018 and was accepted for publication in September 2019. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

© Queen's Printer and Controller of HMSO 2020. This work was produced by Gilson *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Editor-in-Chief of *Health Technology Assessment* and NIHR Journals Library

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

NIHR Journals Library Editors

Professor John Powell Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Senior Clinical Researcher, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor Andrée Le May Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, PGfAR, PHR journals

Professor Matthias Beck Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont Senior Scientific Adviser (Evidence Use), Wessex Institute, University of Southampton, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Wellbeing Research, University of Winchester, UK

Professor John Norrie Chair in Medical Statistics, University of Edinburgh, UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk