ORIGINAL RESEARCH ARTICLE

Appl Health Econ Health Policy 2012; 10 (2): 87-97
1175-5652/12/0002-0087/$49.95/0

Evaluating the Epidemiology and Morbidity Burden Associated with Human Papillomavirus in Israel

Accounting for CIN1 and Genital Warts in Addition to CIN2/3 and Cervical Cancer

Oren Shavit,[1] *Raanan Raz,*[2] *Michal Stein,*[3] *Gabriel Chodick,*[2,4] *Eduardo Schejter,*[5] *Yehuda Ben-David,*[6] *Raanan Cohen,*[3] *Daphna Arbel*[3] and *Varda Shalev*[2,4]

1 The School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel
2 Medical Informatics, Maccabi Healthcare Services, Tel Aviv, Israel
3 MSD Israel Co. Ltd, Hod-Hasharon, Israel
4 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
5 Tel-Aviv Women's Health Center, Maccabi Healthcare Services, Tel Aviv, Israel
6 Division of Gynecologic Oncology, HaEmek Medical Center, Afula, Israel

Abstract

Background: Human papillomavirus (HPV) infection is mostly associated with cervical cancer (CC). However, it can cause other illnesses as well, all of which impact on people's wellbeing and consume healthcare resources. Measures for prevention or early detection of these conditions differ in their effectiveness and cost. An informative evaluation of the projected benefit of these measures depends on understanding the current unmet need, not only limited to CC.

Objective: To evaluate the burden of HPV-related conditions in Israel, including CC, cervical precancerous lesions and genital warts.

Methods: A retrospective database analysis was conducted for the second largest health management organization (HMO) in Israel, covering approximately 1.8 million people. Records were drawn following a search for key words indicative of related diagnoses, lab results, medications, or procedures for the time period of 2006–2008. Prevalence, incidence and resource utilization were analysed. Findings were extrapolated to the whole Israeli population using age and gender incidence rates.

Results: Incidence of CC was found to be 5 per 100 000 females. Incidences of cervical intraepithelial neoplasia (CIN) grades 1, 2 and 3 were 74, 27 and 36 per 100 000 females, respectively. Incidence of genital warts was 239 and 185 per 100 000 for men and women, respectively. The overall annual economic burden was calculated to be $US48 838 058 (year 2010 values).

Conclusions: HPV poses a significant burden in terms of health (clinical and quality of life) and in monetary terms, even for conditions that are sometimes

regarded as benign, such as CIN1 or genital warts. Current findings should be used for proper evaluation of measures to reduce HPV-related morbidity and mortality, such as regular screening and vaccination.

Key points for decision makers

- HPV morbidity poses a significant burden to the Israeli society, both in terms of health (clinical and quality of life) and in monetary terms
- Conditions that are sometimes regarded as minor, such as genital warts or grade 1 cervical intraepithelial neoplasia (CIN1), encompass a burden that should not be ignored
- HPV-related morbidity (including genital warts and CIN1) justifies a comprehensive examination of measures to reduce it, despite a relatively low incidence of cervical cancer in Israel

Background

Human papillomavirus (HPV) infection is mostly associated with cervical cancer.[1] However, the virus, comprised of a family of approximately 100 types,[2] can cause other illnesses as well, including other genital cancers, mouth and oropharyngeal cancers and non-malignant conditions such as genital warts (GW) and juvenile recurrent respiratory papillomatosis (RRP).[3-6]

Some of the HPV-related health states, such as abnormal results of screening tests or grade 1 cervical intraepithelial neoplasia (CIN1), may not be conclusively defined as illnesses. These conditions do not necessarily indicate a progression to cancer and do not mandate treatment, other than follow-up.[7-9] Other non-malignant states, such as GW, might be perceived as benign and self-contained.

Nevertheless, all these 'non-cancerous states' do entail impairment to the person's quality of life. This could be derived from related anxiety, need for additional tests and, as in the case of GW, inconvenience and deprivation of social activities.[10-14] In addition, these states require utilization of health resources such as physician visits, drugs and tests, thus increasing health expenditure.[15]

Screening for HPV is currently included in the Israeli national reimbursement scheme for women aged 35 years and over to use once every 3 years. In addition to screening, another potential measure to reduce HPV-related morbidity is vaccination. Two vaccines are available in Israel. One is a bivalent vaccine (Cervarix®, GlaxoSmithKline), comprised of HPV types 16 and 18, both major causes of cervical cancer.[16] The other is a quadrivalent vaccine (Gardasil®, Merck & Co., Inc.), comprised of HPV types 16 and 18, as well as types 6 and 11, the primary causes of HPV-related GW.[17]

An economic evaluation that was conducted for the Israeli healthcare setting found the vaccination to be cost effective when its price per dose was lower than $US96.85 (year 2007 values).[18] Nevertheless, both vaccines are not yet reimbursed in Israel under the national health insurance scheme. It is plausible that one of the main factors influencing the decision to decline reimbursement is the incidence of cervical cancer in Israel (6 per 100 000 females[19]), which is considered low.[20] This is apparent despite similar prevalence of precancerous states reported in other countries, and similar distribution of affecting virus types.[21,22] In Israel, approximately 40% of cervical cancer patients die from the disease (mortality rate of 2 per 100 000),[23,24] which is similar to other countries.[25,26]

When making decisions regarding allocation of public resources to health technologies, a broad perspective should be taken. This does not only include severe events such as cancer, but also

more benign states such as abnormal Pap results or GW, as all these conditions affect people's wellbeing as well as health resource utilization and expenditure. However, data regarding prevalence and incidence of CIN1, CIN2, or GW in Israel are lacking.

Objective

The objective of this study was to evaluate the burden of HPV-related conditions in Israel through evaluation of the epidemiology of HPV-related cervical cancer, cervical pre-cancerous lesions (CIN of grades 1, 2 and 3) and GW, analysing related resource utilization and estimating impact on quality of life.

Methods

A retrospective database analysis was conducted in April 2010, utilizing the comprehensive longitudinal database of the second largest health management organization (HMO) in Israel (Maccabi Healthcare Services [MHS]), covering approximately 1.8 million individuals. Findings were extrapolated to the whole Israeli population using age and gender incidence rates as described in the Extrapolation to the Total Israeli Population section.

Maccabi Healthcare Services Database Characteristics

MHS has a nationwide network of over 3000 physicians operating in over 4000 clinics who use the MHS computerized medical record (CMR). The database is not only a billing tool but also a central data repository, retaining historical records of patient demographic, clinical and resource-utilization data.[27,28] By using the unique national identity numbers, these data are available at the level of the individual member.[27]

Study Population and Data Extraction

The study population included all members who joined MHS up until January 2006. The analysis was conducted for the time period of 2006–2008. This time frame was chosen to allow for a 3-year period in order to capture routine HPV screening according to practice guidelines.

Four elements within the CMR were screened: (a) clinical files; (b) pharmacy data; (c) central laboratory data; and (d) complementary insurance claims.

Recorded demographic data included age, gender, place of residence and year of immigration. Clinical diagnoses were extracted as follows: cervical cancer cases were retrieved from the National Cancer Registry for MHS members. Data pertaining to abnormal Pap tests, CIN 1, 2 and 3, were extracted from the central lab records. Diagnoses of GW were extracted from physicians' files using ICD-9 code 0.78.11 (condyloma accuminatum) and MHS' corresponding internal codes. Designated HPV procedures included Pap, cervical biopsies, conizations, colposcopies and removal of GW. Procedures and diagnoses that might have been related to HPV but for which this relationship could not be verified through the database (i.e. hysterectomy, oral, penile or vulvar cancer, etc.), were not included in this analysis.

Analysis

Each of the diagnoses was counted for each of the years, as an average over the 3 years, and according to age groups for the 3-year time period. Each diagnosis, except for GW, was counted only once per person over the 3-year time period, with no recurrences allowed in the analysis.

In order to calculate incidence of GW, all persons diagnosed as having GW during 2007 were selected. Those who had an indication of a GW diagnosis or related procedure during 2006 were excluded, as well as those who were not members of MHS for the full 2-year period (2006–2007). Then, the number of cases was counted, allowing for only one case per person (i.e. no recurrence over the year was allowed). Similarly, the number of procedures and individuals experiencing each of the diagnoses or procedures were counted for each of the 3 years as an average across the whole period and according to age groups.

Diagnoses (i.e. CINs, cervical cancer, abnormal Pap and GW) were broken down to their

resource-level components (i.e. physician visits, conizations, drugs, hospitalization days, etc.) using expert opinion that was sought through the following process: a table relating health states with potential resources was personally presented to five gynaecologists (two more declined participation due to time constraints) who were selected according to their work environment (community vs hospital settings), and geographic location. Each was asked to review the table inputs. Once all tables were collected, inputs were averaged to create the resource utilization table (see table S1, Supplemental Digital Content [SDC], http://links.adisonline.com/APZ/A48). This was then used to calculate the economic burden as described in the section on Evaluating the Total Burden.

The distribution of cervical cancer stages was taken from a local study.[29] Breaking down the diagnosis event into its components referred only to additional resource utilization. For example, when addressing an abnormal Pap test, the first physician visit in which the Pap smear was taken was not counted, as it is related to any Pap test. Only additional physician visits that resulted from the abnormal finding, and only for those cases that were not later diagnosed as CIN or cervical cancer (in order to prevent double counting) were counted for each event of abnormal Pap. In addition, for costing purposes, components that were counted distinctively as part of the analysis (i.e. Pap tests, conizations, colposcopies, cervical biopsies, laser evaporations) were not included in the event cost in order to prevent double counting. Then, the economic burden was calculated by assigning price tags to each of the resources utilized and multiplying it by the average annual frequency it was used. Unit cost was taken from formal Israeli tariffs.[30] Prices were calculated in Israeli Shekels (ILS) and converted to $US using an exchange rate of $US1 = ILS3.7. The year of valuation was 2010.

Extrapolation to the Total Israeli Population

The Israeli National Health Insurance Law states that every resident is entitled to healthcare services funded by the state and provided by one of four sick funds (SFs) operating as not-for-profit HMOs.[31] Each resident chooses which of the four SFs to become a member of. Additional health services are covered by complementary health insurance plans, some of which are provided by the SFs and others by private insurers. MHS is the second largest SF of the four, covering approximately 25% of the total Israeli population.[32] The age distribution of MHS members is similar to that of the whole Israeli population despite a small tendency to have members of younger ages. Consequently, the MHS population could be regarded as representative of the Israeli population.

Age- and gender-adjusted incidence rates were used in order to extrapolate findings from the MHS database analysis regarding diagnoses (i.e. abnormal Pap, CINs, cervical cancer and GW), to the total Israeli population. Distribution of the Israeli population by age and gender groups were taken from the Israel Central Bureau of Statistics.[33]

In order to extrapolate utilization of procedures, the following method was used: the percent of people having a procedure, stratified by age and gender, was sought, as well as the average number of procedures per person. These rates were then applied to the matching age and gender groups of the total Israeli population.

Evaluating the Total Burden

The calculated event cost was multiplied by the number of events that was projected to the Israeli population, and summed up with the projected utilization of procedures that were distinctively counted in the MHS database analysis. Only direct medical costs were accounted for. Non-medical and indirect costs (i.e. lost work productivity) are beyond the scope of the current analysis.

To account for the quality-of-life burden related to HPV, QALY weights were assigned to each of the diagnoses. Weights and duration of the corresponding health condition were taken from the study by Annemans et al.[14] evaluating the cost effectiveness of HPV vaccination in Belgium and are presented in table I. Disutility (1-utility weight) was multiplied by the duration of the health state. The frequency of the health states by age and

Table I. QALY weights for the relevant diagnoses, based on Annemans et al.,[14] and calculated disutility due to human papillomavirus-related morbidity using frequency of events by age and gender as found in the current analysis and age-adjusted utility weighing factors from the Israeli Ministry of Health Guidelines for submission of reimbursement requests for health technologies[34]

Health state	Utility weight	Time with the health state	Disutility	Weighted disutility	Annual frequency	QALY lost
Routine screening – Pap smear	0.98	1 mo	0.02	0.00167	328 365	484
Abnormal Pap	0.93	2 mo	0.08	0.0125	15 743	177
Genital warts	0.91	85 d	0.09	0.02096	17 430	337
CIN1 – phase 1	0.91	2 mo	0.09	0.015	2 545	35
CIN1 – phase 2 (follow up)	0.96	10 mo	0.04	0.03333	2 545	78
CIN2	0.87	2 mo	0.13	0.02167	906	18
CIN3	0.87	2 mo	0.13	0.02167	1 198	23
Cervical cancer	0.56	5 y	0.44	2.1755	177	316
Overall						**1468**

CIN = cervical intraepithelial neoplasia.

gender was multiplied by the corresponding disutility and by age- and gender-utility weighing factors, which are used by the Israeli Ministry of Health.[34] A summation of all disutilities gave the overall QALYs lost due to HPV-related morbidity. It should be stated that mortality-related disutility was not accounted for in this analysis.

Results

The study population included, on average, 1 765 481 persons per year, of whom 52% were women. On average, 110 592 women had undergone Pap tests per year, with an average of 115 125 tests performed. The highest usage of Pap was found in the age group of 30–40 years (figure 1). Although reimbursement is granted under the national reimbursement scheme only for women between the ages of 35 and 54 years (unless a clinical indication justifies differently), 53% of women between the ages of 20 and 35 years and 28% of women between the ages of 55 and 64 years were found to have taken a Pap test with the MHS over a 3-year period, on average. On the other hand, only 50% of women between the ages of 35 and 54 years were found to take at least one Pap screening test over the time period. Following these Pap tests, 4911 abnormal Pap were identified, on average, per year. This means that for every 23 Pap tests performed, one would result as abnormal.

The utilization frequency of the procedures is presented in table II.

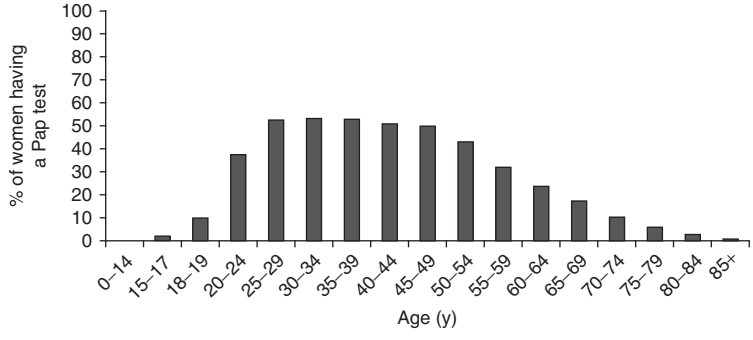

Fig. 1. Percentage of women having a Pap test over a 3-year time period (2006–2008) by age group at Maccabi Healthcare Services.

Table II. Calculated costs of diagnoses/events and the weighted cost used for overall burden calculation, after omitting costs of procedures that were separately and distinctively counted in the analysis, such as colposcopies, biopsies, etc. (Calculated in Israeli Shekels [ILS] and converted to $US using an exchange rate of $US1 = ILS3.59; year 2010 values)

Resource/diagnosis	Unit cost ($US)	Unit cost for burden calculation ($US)	Average annual occurrences in MHS	Projected annual occurrences in Israel	Projected annual economic burden in Israel ($US)
Pap	62[a]	62	115 125	328 365	20 358 643
Colposcopy	67[b]	67	15 485	44 870	3 006 303
Conization	928	928	664	2 371	2 199 944
Biopsy	455	492	3 081	11 049	5 436 185
Laser evaporation	881	918	721	2 656	2 437 918
Prescriptions	45	45	2 735	10 466	470 962
Abnormal Pap	567	104	4 911	15 743	1 637 288
CIN1	801	346	669	2 545	880 509
CIN2	1 964	398	241	906	360 514
CIN3	2 122	285	329	1 198	341 402
Cervical cancer[c]	17 410	15 601	46	177	2 763 846
Genital warts, men	495	495	2 988	9 704	4 803 649
Genital warts, women	536	536	2 346	7 726	4 140 896
Total					48 838 058

a Comprises $US26 for the Pap smear and $US36 for the physician visit and assuming this cost also covers laboratory expenses.

b Comprises $US31 for the colposcopy and $US36 for the physician visit.

c See table III.

CIN = cervical intraepithelial neoplasia; **MHS** = Maccabi Healthcare Services

Cervical Cancer and Precancerous States

The analysis retrieved diagnoses of 669 CIN1, 241 CIN2, 329 CIN3 and 46 cervical cancer cases, on average, per year at MHS (figure 2). The incidence rates for these conditions were calculated to be 74, 27, 36 and 5 per 100 000 women per year, respectively. Incidences by age of these events are presented in table S2 in the SDC.

The number of cervical cancer cases retrieved from the Israeli National Cancer Registry for MHS was 35, 50 and 52 cases for 2006, 2007 and 2008, respectively, with a calculated annual average of 46 cases, reflecting an average incidence rate of 5.03 cases per 100 000 women per year at MHS. This means that for every nine abnormal Pap results, there was one case of CIN2/3, and that for every 108 abnormal Pap results, there was one case of cervical cancer.

The distribution of CINs and cervical cancer cases across age groups (table S2, SDC) showed that CIN1 and CIN2 were most frequent between the ages of 25 and 34 years, while CIN3 peaked about 5 years later. Cervical cancer had two peaks: one in the 35–39-year age group and a more significant peak in the age range of 45–54 years, some 15 years later than the peak of CIN2/3 (figure 3).

Table III. Breakdown of cervical cancer to its stages to allow calculation of the average cost per case of cervical cancer in table II

Stage	Event cost ($US)	% of cancer stages	Adjusted cost for a cervical cancer case ($US)	Adjusted cost for burden analysis calculations ($US)
IAI	5 893	7	413	338
IA2-IIA	18 857	60	11 314	10 036
IIB	20 312	18	3 656	3 393
III-IV	13 513	15	2 027	1 834

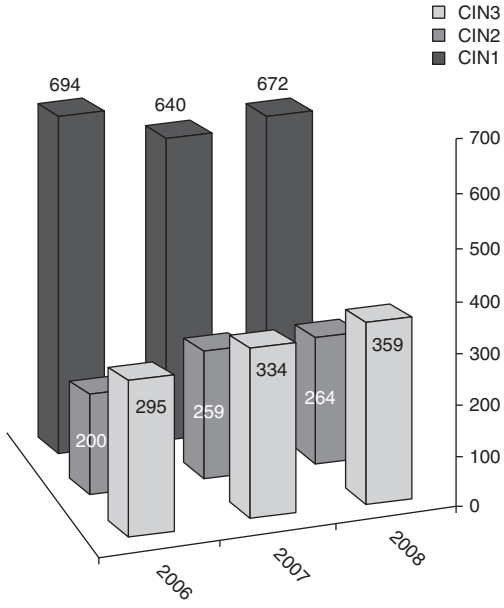

Fig. 2. Number of cases of cervical intraepithelial neoplasia (CIN) grades 1–3 over the 3-year time period (2006–2008).

Genital Warts

There were, on average, 5335 cases of GW per year: 2346 in women and 2988 in men. The incidence rate was higher for men (2.39 per 1000 men) than for women (1.85 per 1000 women). The distribution of GW cases across age groups showed that men experience it several years later than women and to a greater extent (figure 4). The peak of GW cases was shown to occur during the 25–34-year age range, with 971 and 775 cases, on average, for men and women, respectively, per year. On average, 3308 prescriptions for topical treatment of GW (i.e. topical imiquimod or podophyllotoxin) were issued per year at MHS.

Extrapolation to the Israeli Population

Extrapolation of the findings to the total Israeli population (approximately 7.3 million people) projected utilization of 328 365 Pap smears, 44 870 colposcopies, 2371 conizations, 11 049 cervical biopsies, 2656 laser evaporations under colposcopy and 10 466 GW-related prescriptions per year. In addition, 15 743 abnormal Pap tests, 2545 CIN1, 906 CIN2, 1198 CIN3, 177 cervical cancers and 17 430 GW cases were projected per year.

Cost

As mentioned in the analysis section, health states were broken down into their procedural components using expert opinion (table S1 in the SDC). Age distribution to account for different cervical cancer treatments was taken from the results of the current study: 7% of patients were older than 70, and 11% were younger than 35 years of age. The resulting event cost and weighted cost (i.e. after omitting procedures that were distinctively counted) for each of the conditions is presented in table II. The calculated annual cost of procedures was found to be $US33 909 954. The annual cost of GW was calculated to be $US8 944 545. The calculated overall annual economic burden of HPV in Israel was calculated to be $US48 838 058.

QALYs

Multiplying the age- and gender-adjusted disutility weights (1-utility weight) by the time the diagnosis is experienced and by the projected annual frequency of the diagnosis (also by age and gender) indicated a potential annual loss of 1468 QALYs for the Israeli population of 7.3 million

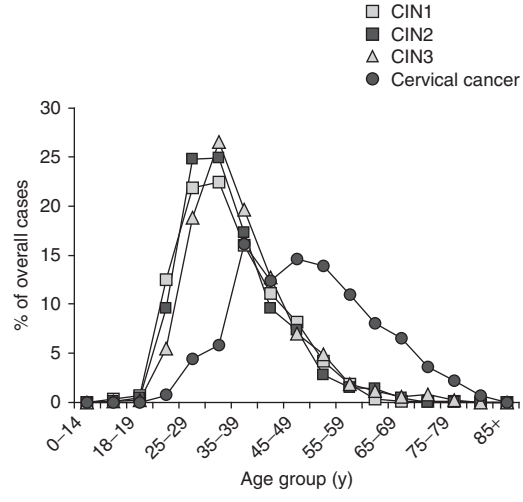

Fig. 3. Distribution of cervical intraepithelial neoplasia (CIN) grades 1–3 and cervical cancer cases across age groups as the rate of total cases per category.

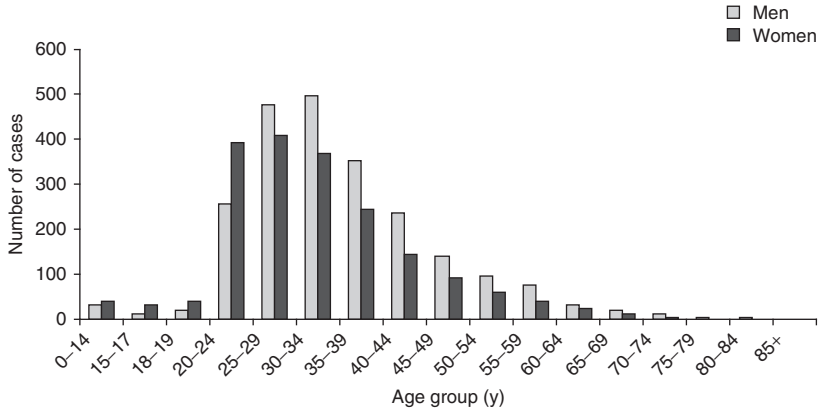

Fig. 4. Distribution of GW cases across age groups (annual average for the 3-year time period) at Maccabi Healthcare Services.

(table I). A sensitivity analysis for cervical cancer[35] and GW[11,15] disutility weights varied the overall QALYs lost between 1142 and 1501 (table IV).

Discussion

This is the first population-based study to examine the incidence of CIN by distinct grade (including CIN1) and of GW, for a large-scale sample of the population in Israel. Analysing the comprehensive longitudinal computerized database of a large HMO enabled a unique visualization of the epidemiology of HPV-related morbidity.

The current analysis showed that despite the relatively low incidence of cervical cancer in Israel, the overall burden related to HPV is substantial, with an annual healthcare resource utilization value of approximately $US49 million, and impairment to quality of life equivalent to a loss of 1468 QALYs, for the Israeli population of 7.3 million. This burden could be viewed in light of the annual national health expenditure of approximately $US17 billion in Israel and that of $US8 billion of public expenditure for financing the National Health Services Basket.[36]

The average incidences of CIN grades 1, 2 and 3 were 74, 27 and 36 cases per 100 000 women per year, respectively. This incidence is lower than that found in a US study (160 and 120 per 100 000 for CIN1 and CIN2/3, respectively).[37] However, the methodology of the two studies differs significantly and limits a comparison of the findings. In fact, we could not find a recent comprehensive epidemiological study that referred to the incidence of the distinct CIN states and GW in the English language peer-reviewed literature, in order to compare our current results. This emphasizes the importance of the current study.

Table IV. Results of the sensitivity analysis for QALYs lost using disutility weights for cervical cancer (CC) as used by Kim & Goldie[35] (0.76 for local, 0.67 for regional and 0.48 for distal CC, respectively, weighted by the conditions' distribution among Israeli women), and disutility weights for genital warts (GW) as found by Woodhall et al.[11,15]

	Weighted disutility for GW	Weighted disutility for CC	QALYs lost due to GW	QALYs lost due to CC	QALYs lost due to HPV-related morbidity
Base case	0.021	2.18	337	316	1468
CC disutility reduced	0.021	1.75	337	254	1406
GW disutility reduced	0.0045	2.18	72	316	1204
GW disutility increased	0.023	2.18	370	316	1501
Best case: CC and GW disutilities reduced	0.0045	1.75	72	254	1142

HPV = human papillomavirus.

The incidence of cervical cancer found in the current study (5.03 per 100 000) is lower than the national incidence reported by the Israeli National Cancer Registry (6.11 per 100 000).[19] It should also be noted that in the current analysis there is an apparent 'leap' in the absolute number of cervical cancer cases, from 35 in 2006 to 50 and 52 in 2007 and 2008, respectively, which is not in line with the steady incidence rate over time described by the National Cancer Registry.[38] These discrepancies may indicate that the cervical cancer burden found in the current analysis is actually an underestimation of the true burden.

Disutility weights vary between sources. When more conservative weights were used for GW and for cervical cancer (i.e. 0.03 instead of 0.09 for GW, and 0.35 instead of 0.44 for cervical cancer),[15,39] then the overall disutility was equal to a loss of 1197 QALYs (vs 1468 in the base case).

In order to put the disutility related to HPV morbidity into perspective, we looked at QALY weights assigned to other disease states.[40] It can be seen (figure 5) that the utility assigned to an abnormal Pap result is similar to that of a urinary tract infection and lower than that related to hypertension. CIN1 appears to have two phases of hampered quality of life. The first has a utility similar to that of GW which is similar to that of well controlled asthma. The second phase represents a return to a state of almost complete health. CIN2/3 has a utility weight similar to having an event-free percutaneous coronary intervention. In addition, when summed up, GW cases were found to cause a similar loss of QALYs as cervical cancer cases, probably due to their greater frequency (table I).

The results of this study should also be considered in light of its limitations. First, being a retrospective database analysis, associations could not be taken for cause and effect explanations. Furthermore, data regarding potential risk factors for HPV morbidity (i.e. smoking, number of sexual partners) are not documented in the database and could not be analysed for associations.

Second, significant events such as hysterectomies, non-cervical cancers, other complications (i.e. RRP) and deaths that could be HPV-driven were not accounted for, as the relationship to HPV could not be established in the database. This may indicate that the current analysis underestimated the true burden of HPV. Third, the relatively short time frame of the analysis together with the nature of the retrospective database analysis limits the ability to analyse incidence trends over time.

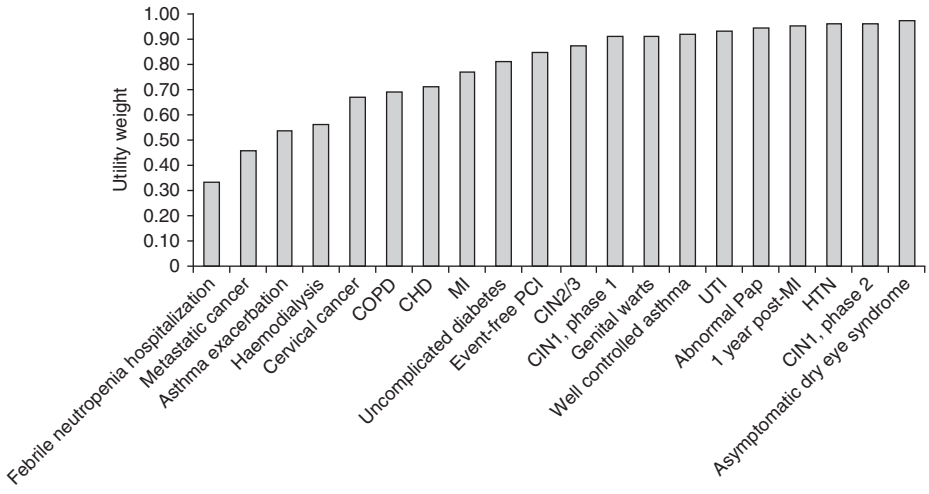

Fig. 5. Utility weights of human papillomavirus-related states in light of other selected health states (based on the cost-effectiveness analysis registry of Tufts Medical Center's Institute for Clinical Research & Health Policy Studies[37]). **CHD** = coronary heart disease; **CIN** = cervical intraepithelial neoplasia; **COPD** = chronic obstructive pulmonary disease; **HTN** = hypertension; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **UTI** = urinary tract infection.

Fourth, extrapolation of findings from MHS to the total population was based on age- and gender-specific incidence rates. Even though the MHS population is similar in age and gender distribution to the total Israeli population, it might be somewhat different in socioeconomic status, ethnicity (i.e. Jews, Arabs) and sector (secular, conservative, orthodox, etc.) distribution, which might cause some impairment to results extrapolation. Fifth, only direct medical costs were accounted for, and no disutility was assigned to HPV-related death, which may result in underestimation of the true burden of HPV-related morbidity and mortality.

Conclusions

HPV morbidity poses a significant burden to the Israeli society, in terms of health, quality of life and in monetary terms. This study showed that HPV-related morbidity, including GW and CIN1, justifies a comprehensive examination of measures to reduce it, such as regular screening aimed at reducing cancerous states, and immunization to address prevention of these states and of GW.

Acknowledgements

This study was supported by an unrestricted grant from MSD Israel. Dr Stein, Dr Cohen and Ms Arbel are employees of MSD Israel; Dr Shavit received consultancy fees from MSD Israel; Dr Shalev, Dr Chodik and Dr Raz are employees of Maccabi Healthcare Services sick fund, which owns the database that was used, and do not have any financial ties with MSD Israel.

References

1. Garland SM, Smith JS. Human papillomavirus vaccines: current status and future prospects. Drugs 2010; 70 (9): 1079-98
2. de Villiers EM, Fauquet C, Broker TR, et al. Classification of papillomaviruses. Virology 2004; 324 (1): 17-27
3. Wiley D, Masongsong E. Human papillomavirus: the burden of infection. Obstet Gynecol Surv 2006; 61 (6 Suppl. 1): S3-14
4. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. Vaccine 2006; 24 Suppl. 3: S3/11-25
5. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine 2006; 24 Suppl. 3: S3/35-41
6. Gross G, Pfister H. Role of human papillomavirus in penile cancer, penile intraepithelial squamous cell neoplasias and in genital warts. Med Microbiol Immunol 2004; 193 (1): 35-44
7. Bosch FX, Burchell AN, Schiffman M, et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine 2008; 26 Suppl. 10: K1-16
8. Wright Jr TC, Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. J Low Genit Tract Dis 2007; 11 (4): 223-39
9. Wright Jr TC, Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis 2007; 11 (4): 201-22
10. Mortensen GL, Larsen HK. The quality of life of patients with genital warts: a qualitative study. BMC Public Health 2010; 10: 113
11. Woodhall S, Ramsey T, Cai C, et al. Estimation of the impact of genital warts on health-related quality of life. Sex Transm Infect 2008; 84 (3): 161-6
12. Mortensen GL. Long-term quality of life effects of genital warts: a follow-up study. Dan Med Bull 2010; 57 (4): A4140
13. Insinga RP, Glass AG, Myers ER, et al. Abnormal outcomes following cervical cancer screening: event duration and health utility loss. Med Decis Making 2007; 27 (4): 414-22
14. Annemans L, Remy V, Oyee J, et al. Cost-effectiveness evaluation of a quadrivalent human papillomavirus vaccine in Belgium. Pharmacoeconomics 2009; 27 (3): 231-45
15. Woodhall SC, Jit M, Cai C, et al. Cost of treatment and QALYs lost due to genital warts: data for the economic evaluation of HPV vaccines in the United Kingdom. Sex Transm Dis 2009; 36 (8): 515-21
16. Szarewski A. HPV vaccine: Cervarix. Expert Opin Biol Ther 2010; 10 (3): 477-87
17. Siddiqui MA, Perry CM. Human papillomavirus quadrivalent (types 6, 11, 16, 18) recombinant vaccine (Gardasil). Drugs 2006; 66 (9): 1263-71
18. Ginsberg GM, Fisher M, Ben-Shahar I, et al. Cost-utility analysis of vaccination against HPV in Israel. Vaccine 2007; 25 (37-38): 6677-91
19. Israel National Cancer Registry. Cancer incidence tables - Cervix Uteri, 2007 [online]. Available from URL: http://www.health.gov.il/download/sartan/2007/cer_ut2007.pdf [Accessed 2010 Sep 1]
20. Menczer J. The low incidence of cervical cancer in Jewish women: has the puzzle finally been solved? Isr Med Assoc J 2003; 5 (2): 120-3
21. Sadan O, Schejter E, Ginath S, et al. Premalignant lesions of the uterine cervix in a large cohort of Israeli Jewish women. Arch Gynecol Obstet 2004; 269 (3): 188-91
22. Menczer J. The human papillomavirus vaccine and its relevance in Israel. Isr Med Assoc J 2007; 9 (7): 546-9
23. Israel National Cancer Registry. Cancer in Israel: trends in incidence and mortality 1982-2002 and selected updated data, 2004 [online]. Available from URL: http://www.health.gov.il/Download/pages/cancer290109.pdf [Accessed 2010 Sep 1]
24. Israel Central Bureau of Statistics. Statistical abstract of Israel 2005 [online]. Available from URL: http://www.

cbs.gov.il/reader/shnaton/templ_shnaton.html?num_tab=st02_10x&CYear=2005 [Accessed 2010 Sep 1]

25. World Health Organisation. Cervical cancer, human papillomavirus (HPV), and HPV vaccines. Key points for policymakers and health professionals [online]. Available from URL: http://www.rho.org/files/WHO_PATH_UNFPA_cxca_key_points.pdf [Accessed 2010 Sep 1]
26. Arbyn M, Autier P, Ferlay J. Burden of cervical cancer in the 27 member states of the European Union: estimates for 2004. Ann Oncol 2007; 18 (8): 1423-5
27. Chodick G, Heymann AD, Wood F, et al. The direct medical cost of diabetes in Israel. Eur J Health Econ 2005; 6 (2): 166-71
28. Shalev V, Chodick G, Heymann AD. Format change of a laboratory test order form affects physician behavior. Int J Med Inform 2009; 78 (10): 639-44
29. Menczer J, Kogan L, Schejter E, et al. A population-based study of selected demographic characteristics of Israeli-Jewish women with cervical squamous cell carcinoma. Arch Gynecol Obstet 2011; 283 (3): 629-33
30. Israel Ministry of Health. Health Services tariff, 2010 [online]. Available from URL: http://www.health.gov.il/pages/default.asp?maincat=1&catId=111&PageId=827 [Accessed 2010 Jun 1]
31. Israel Ministry of Health. Israeli Health Insurance Law, 1994 [online]. Available from URL: http://www.health.gov.il/forms/forms.asp?category_id=36&Element_Type_id=6 [Accessed 2010 May 31]
32. National Insurance Institute of Israel. Sick Funds Membership, April 2010 [online]. Available from URL: http://www.btl.gov.il/Mediniyut/Situation/haveruth/Documents/capitatia042010.pdf [Accessed 2010 May 31]
33. Israel Central Bureau of Statistics. Statistical abstract of Israel, 2009 [online]. Available from URL: http://www.cbs.gov.il/shnaton60/st02_19.pdf [Accessed 2010 Jun 1]
34. Israel Ministry of Health. Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services, 2011 [online]. Available from URL: http://www.health.gov.il/pages/default.asp?maincat=11&catid=291&pageid=2133 [Accessed 2011 Jul 1]
35. Kim JJ, Goldie SJ. Cost effectiveness analysis of including boys in a human papillomavirus vaccination programme in the United States. Br Med J 2009; 339: b3884
36. Israel Central Bureau of Statistics. National expenditure on Health, 2011 [online]. Available from URL: http://www.cbs.gov.il/hodaot2010n/08_10_201e.pdf [Accessed 2011 Apr 1]
37. Henk HJ, Insinga RP, Singhal PK, et al. Incidence and costs of cervical intraepithelial neoplasia in a US commercially insured population. J Low Genit Tract Dis 2010; 14 (1): 29-36
38. Israel Ministry of Health. Israel national cancer registry, 2002 [online]. Available from URL: http://www.health.gov.il/pages/default.asp?PageId=688&catId=56&maincat=22 [Accessed 2008 Sep 1]
39. Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. N Engl J Med 2008; 359 (8): 821-32
40. Center for the Evaluation of Value and Risk in Health. CEA Registry, 2010 [online]. Available from URL: https://research.tufts-nemc.org/cear/Default.aspx 2010; [Accessed 2010 Aug 1]

Correspondence: Dr *Oren Shavit*, Division of Clinical Pharmacy, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, POB 12065, Jerusalem 91120 Israel.
E-mail: orens@ekmd.huji.ac.il

