Do cervical cancer data justify HPV vaccination in India? Epidemiological data sources and comprehensiveness

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Summary

The Indian government suspended research in April 2010 on the feasibility and safety of human papillomavirus (HPV) vaccine in two Indian states (Andhra Pradesh and Gujarat) amid public concerns about its safety. This paper describes cervical cancer and cancer surveillance in India and reviews the epidemiological claims made by the Programme for Appropriate Technology in Health (PATH) in support of the vaccine in these two states. National cancer data published by the Indian National Cancer Registry Programme of state registry returns and the International Agency for Research on Cancer cover around seven percent of the population with underrepresentation of rural, northern, eastern and north-eastern areas. There is no cancer registry in the state of Andhra Pradesh and PATH does not cite data from the Gujarat cancer registries. Age-adjusted cervical cancer mortality and incidence rates vary widely across and within states. National trends in age standardized cervical cancer incidence fell from 42.3 to 22.3 per 100,000 between 1982/1983 and 2004/2005 respectively. Incidence studies report low incidence and mortality rates in Gujarat and Andhra Pradesh. Although HPV prevalence is higher in cancer patients (93.3%) than healthy patients (7.0%) and HPV types 16 and 18 are most prevalent in cancer patients, population prevelance data are poor and studies highly variable in their findings. Current data on HPV type and cervical cancer incidence do not support PATH's claim that India has a large burden of cervical cancer or its decision to roll out the vaccine programme. In the absence of comprehensive cancer surveillance, World Health Organization criteria with respect to monitoring effectiveness of the vaccine and knowledge of disease trends cannot be fulfilled.

Introduction

Cervical cancer is estimated to cause around 274,000 deaths a year, approximately 80% of which occur in the developing world.[1] Guidelines for cervical cancer screening are implemented in few Indian states.[2] Human papillomavirus (HPV) is associated with cervical cancer. Of the 100 HPV types, 18 have been categorized as high-risk types (hr-HPV) or possible high-risk types for cervical cancer, while the rest are low-risk types (lr-HPV).[3] Cervarix® made by Glaxo SmithKline

(GSK) is a bivalent vaccine that protects against HPV strains 16 and 18, and Gardasil® by Merck is a quadrivalent vaccine that protects the individual against HPV strains 16, 18, 6 and 11. HPV types 16 and 18 are said to account for approximately 70% of all cervical cancer cases in India.[4]

The Programme for Appropriate Technology in Health (PATH), a USA-based not for profit non-governmental organization (NGO), has been undertaking postlicensing observational studies on HPV vaccines in India on coverage, acceptability, feasibility and costs of the vaccines in two Indian states, Gujarat and Andhra Pradesh, funded by the Bill & Melinda Gates Foundation.[5] The study was suspended in April 2010 by the Government of India amid public concerns about safety.[6]

Currently, PATH and the Indian government are investigating whether to implement a HPV vaccination programme. PATH claims that 'in raw numbers, India has the largest burden of cancer of the cervix of any country worldwide'[5] and that the two states were selected 'based on cervical cancer disease burden […] and uptake of other vaccines being in the middle range for certain variables (e.g., immunization coverage)'.[5] The World Health Organization (WHO) advises that the epidemiology of the disease should be known and be of sufficient importance to justify its prioritization, and that surveillance systems should be capable of assessing the impact of a vaccine intervention following its introduction.[7]

This paper describes the key institutions that report on cervical cancer in India and the comprehensiveness of cancer surveillance systems. Secondly, it reviews the nature and strength of the epidemiological evidence with respect to cervical cancer incidence, prevalence, HPV type prevalence and distribution. Lastly, it reviews the strength of the epidemiological evidence used to justify the roll out of the PATH study in the states Gujarat and Andhra Pradesh.

Background to cancer surveillance in india

There is no general account in the literature of cancer surveillance in India. The two main agencies involved in reporting incidence, prevalence and mortality of cervical cancer in India are the National Cancer Registry Programme (NCRP) of India and the International Agency for Research on Cancer (IARC) (Figure 1). Searches were undertaken of the IARC and NCRP website. A more comprehensive search was performed to identify agencies involved in reporting data about cervical cancer incidence, prevalence and mortality by reviewing the WHO website, the website of the government of India, and sources cited as references in articles found in the preliminary literature search below.

NCRP

The NCRP is a network of population-based cancer registries (PBCR) and hospital-based cancer registries (HBCR) in India, under the Indian Council of Medical Research (ICMR).[8] There are 26 PBCRs and six HBCR registered in the network.[8]

NCRP Reports

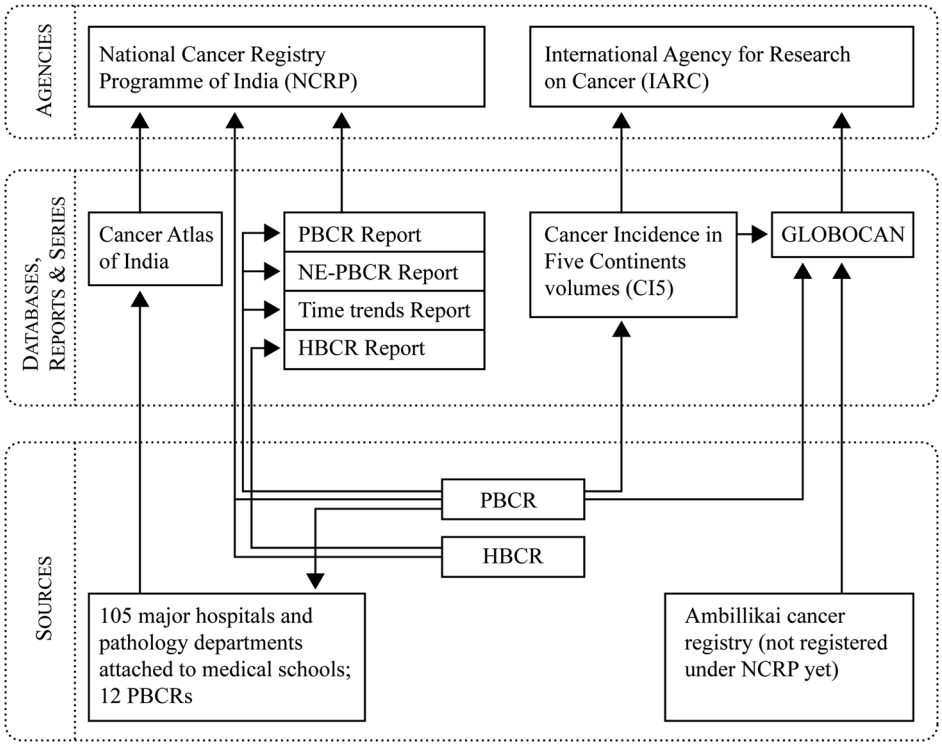
The NCRP compiles data generated by individual registries; these cover approximately 7% of the Indian population but underrepresent rural, northern and eastern regions.[8] Despite active case finding, registered cases are likely to be restricted to groups who have access to healthcare facilities.

The NCRP report on 'Time trends in cancer incidence rates 1982–2005' shows a statistically significant decline in age-adjusted cervical cancer incidence rates in urban registries in India from 42.3 per 100,000 in 1982–1983 to 22.3 per 100,000 in 2004–2005.[8] No time trends in mortality rates are published.

Cancer Atlas of India

The 'Cancer Atlas of India' is used to identify geographical cancer patterns and to enhance coverage of cancer registration using cancer cases registered in pathology departments attached to medical schools and major hospitals as the main source.[8] The Atlas is estimated to cover about 13–21% of all cancer cases in India. The far north and northeast states are underrepresented, although a new Cancer Atlas in Punjab[8] in the north is currently under development. The Atlas represents mainly urban and wealthier India, as its cases are derived from major hospitals and medical

Figure 1
Overview of agencies and sources reporting on cervical cancer incidence and mortality in India



PBCR: Population Based Cancer Registry (NE-PBCR: north-east)
HBCR: Hospital Based Cancer Registry

schools. Incidence rates cannot be extrapolated to the whole of India and under and over-recording of cases has been noted.[9]

IARC

IARC is a WHO affiliate agency that conducts research in all cancers. 'Cancer Incidence in Five Continents' and the 'GLOBOCAN' have been produced by IARC.

Cancer Incidence in Five Continents (CI5)

'Cancer Incidence in Five Continents' (CI5) reports on cancer incidence rates. The 2007 volume drew on data from seven cancer registries in India; not all are registered under the NCRP. The CI5 registries in Chennai, Karunagapally, Mumbai, Nagpur, New Delhi, Pune and Trivandrum mainly represent west, south and central India.[10]

Globocan

IARC also produces the database GLOBOCAN that provides estimates of national cancer incidence and mortality rates in countries all over the world, including India.[11] GLOBOCAN 2008 data for estimating cervical cancer incidence mortality in India draws on data mainly derived from the west and south. Age-adjusted mortality rates are based only on Mumbai and Chennai data. The written methods of GLOBOCAN for India are incomplete and difficult to follow.

Overlapping data and non universal coverage

The NCRP Reports, Cancer Atlas, CI5 and the GLOBOCAN rely on overlapping sources (Figure 1). Cancer incidence data published by the NCRP Reports, the Cancer Atlas of India, the CI5, and

the GLOBOCAN underrepresent east, far north and rural India. Cancer mortality rates published by the NCRP Reports and the GLOBOCAN underrepresent north, west, north-east and rural India. The analysis of the NCRP Reports, the Cancer Atlas of India and the CI5 reveal that although data were of high quality, they are not comprehensive.

Andhra Pradesh and Gujarat

Andhra Pradesh

There is no NCRP or other cancer registry in the state of Andhra Pradesh and neither CI5 nor GLOBOCAN publish data for this state. The Cancer Atlas of India publishes data about Andhra Pradesh, for only two out of 23 districts. Age-adjusted incidence rates are 10.16 in Hyderabad District and 14.29 per 100,000 in Nellore District in 2001/2002.[8]

Gujarat

There are two cancer registries in Gujarat, one urban and one rural, which cover only the Ahmedabad district. These registries under the Gujarat Cancer and Research Institute contribute to the NCRP. The rural registry shows an age-adjusted incidence rate of 8.5 per 100,000 (2006/2008),[8] the urban registry an age-adjusted incidence rate of 9.1 per 100,000 (2006/2008)[8] and a mortality rate of 1.8 per 100,000 in 2004/2005. The coverage of the registries is about 18.9 million people.

The Cancer Atlas of India provides reliable data for 6 of the 25 districts in Gujarat. Minimum age-adjusted incidence rates vary from 2.99 to 8.99 per 100,000 between states in 2001/2002.[8]

Although older volumes of the Cancer Incidence in Five Continents (CI5) report on cancer incidence in Gujarat (Ahmedabad), the latest volume does not. The incidence rates in these volumes are however extracted from the NCRP.[8,10]

The GLOBOCAN does not publish any separate data for Gujarat.

PATH does not cite any of the data on Andhra Pradesh or Gujarat; Gujarat has low incidence rates and few data on mortality rates are available.

Nature and quality of epidemiological evidence in cervical cancer and HPV types

Methods

The five studies cited by PATH were analyzed and a further search was conducted to ascertain cervical cancer incidence and mortality, and HPV types in India. Pubmed, Medline, Web of Knowledge and EMBASE with the following search terms:

'(cervical cancer OR uterine cervical neoplasm OR human papillomavirus OR HPV) AND (burden OR disease burden OR incidence OR prevalence OR mortality) AND (India)'

'HPV prevalence' and 'HPV type distribution' were added to the search for more specific information on these two topics.

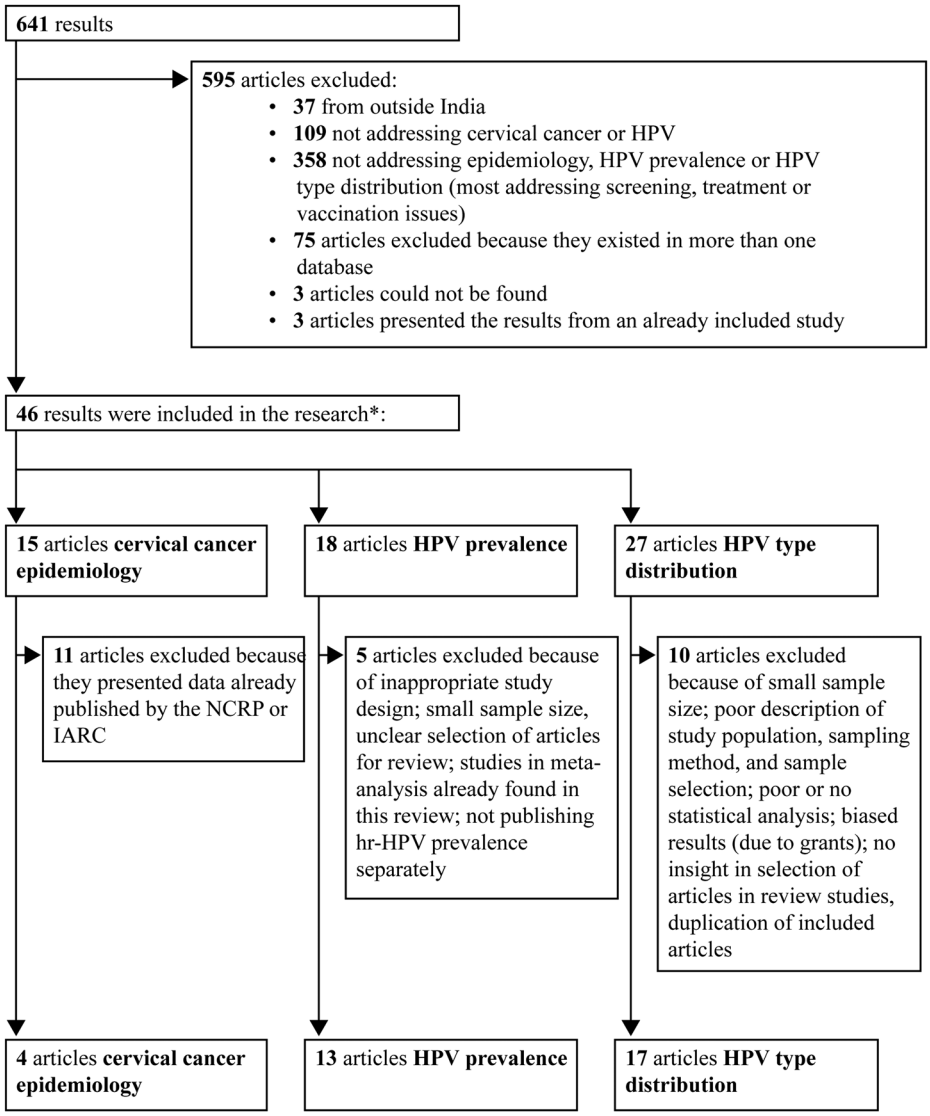
Results

The search was restricted to articles published between January 2000 and March 2012 in the English language. A total of 641 articles were found; of which 595 articles were excluded because they were from outside India or they did not address the epidemiology of cervical cancer or HPV prevalence or type distribution. Other articles were excluded because there were duplications between databases or articles could not be found (Figure 2).

The remaining 46 articles were allocated as follows: cervical cancer epidemiology, HPV prevalence, or HPV type distribution.

Of the 15 articles dealing with cervical cancer epidemiology, nine were excluded because they presented data already published by NCRP or IARC. The recent *Lancet* article reporting on mortality rates was excluded for a number of reasons. It is based on a sample survey of deaths in a million homes undertaken between 2001 and 2003 using verbal autopsies. The study itself generated very small numbers on cervical cancer deaths overall and over a large number of areas. There are problems over coder agreement, quality and accuracy of data, and a sensitivity analysis was not performed. Moreover these data are then extrapolated to the whole population of India and projected forward to 2010, which in itself is problematic because of changing cancer

Figure 2
Inclusion and exclusion criteria in the combined literature search on cervical cancer epidemiology, HPV prevalence and HPV type distribution



patterns.[12] Of the 18 studies on HPV prevalence, five were excluded because one review presented studies already identified in the literature search, a second review did not assess quality, and a third had a small sample size, did not match its cases and controls, and worked with a significance level of 20%. Two other studies were excluded because they only published overall HPV prevalence, no separate numbers for high-risk HPV or individual HPV type prevalence.

Of the 27 studies dealing with HPV type distribution, ten articles were excluded because of a poorly described sampling method, small sample sizes, poor description of study population, absence of statistical analysis, or duplication of presented materials of included articles.

PATH

Epidemiological sources

The PATH strategy document 'Shaping a Strategy to Introduce HPV Vaccines in India: Results from the HPV Vaccines' states that 'in raw numbers, India has the largest burden of cancer of the cervix of any country worldwide'. This claim is not supported by the references,[5] moreover data from the cancer registries in Gujarat or the Cancer Atlas were not cited.

PATH selected Andhra Pradesh and Gujarat 'based on cervical cancer disease burden' and because they were 'in the middle range for certain variables (e.g., immunization coverage)'.[5] There are no references provided for this statement.

Of the five studies[8,13–15] that PATH cites in relation to cervical cancer or HPV epidemiology, one study could not be traced; the HBCR report is not comprehensive and does not provide age-adjusted cervical cancer incidence rates;[8] and the three remaining studies[13–15] did not examine epidemiology of cancer but reported on HPV prevalence and type distribution. Only one study was conducted in Andhra Pradesh[15] and none in Gujarat. The three studies were conducted in rural populations in the south, and urban populations in the south and north of India.

Table 1
Latest available data on incidence and mortality ratios of cervical cancer in India categorised according to location

Location	*Age-adjusted incidence ratio per 100,000 population*	*Age-adjusted mortality ratio per 100,000 population*	*Year (incidence rate and mortality rate respectively)*	*Rural/urban*	*Area*
Aizawl District	22.5	7.5	2006–2008; 2005–2006	Rural	North-east
Ahmedabad Rural	8.5	/	2006–2008	Rural	West
Ahmedabad Urban	9.1	1.8	2006–2008; 2004–2005	Urban	West
Ambilikkai	22.1	/	2003–2006	Rural	South
Aurangabad	13.8	/	2006–2008	Urban	Central
Bangalore	21.1	3.7	2006–2008; 2004–2005	Urban	South
Barshi Expanded	18.9	/	2006–2008	Rural	West
Barshi rural	18.6	/	2006–2008	Rural	West
Bhopal	18.9	1.6	2006–2008; 2004–2005	Urban	Central
Cachar district	11.2	/	2006–2008	Rural/urban	North-east
Chennai	18.5	7.7	2006–2008; 2004–2005	Urban	South
Delhi	17.9	0.9	2006–2008; 2004–2005	Urban	North
Dibrugarh District	6.1	0.2	2006–2008; 2005–2006	Rural/urban	North-east
Imphal West District	16.3	/	2006–2008	Urban	North-east
Kamprup Urban District/ Guwahati	14.6	1.2	2006–2008; 2005–2006	Urban	North-east
Karunagapally	10.6	/	1998–2000	Rural	South
Kashmir Valley	0.9	/	2002–2006	Rural/urban	North
Kollam	8.3	/	2006–2008	Rural	South
Kolkata	14.2	/	2006–2008	Rural/urban	North-east
Manipur State (MR)	9.4	/	2006–2008	Rural/urban	North-east
MR – Excl. Imphal West	7.4	/	2006–2008	Rural	North-east
Mizoram State (MZ)	17.7	4.8	2006–2008/2005–2006	Rural/urban	North-east
MZ – Excl. Aizawl	14.8	3.2	2006–2008; 2005–2006	Rural/urban	North-east
Mumbai	14.1	4.5	2006–2008; 2004–2005	Urban	West
Nagpur	14.7	/	2006–2008	Urban	Central
Pune	12.4	/	2006–2008	Urban	West
Sikkim State	10.9	2.8	2006–2008; 2005–2006	Rural/urban	North-east
Silchar	12.1	0.7	2005–2006	Rural/urban	North-east
Thiruvananthapuram	8.8	/	2006–2008	Urban	South

Cervical incidence and mortality data

Of the four studies identified in the literature review addressing cervical cancer incidence and mortality data, none was conducted in Andhra Pradesh or Gujarat.[16–19]

Two studies were of the Dindigul Ambilikkai Cancer Registry in Tamil Nadu (not registered under the NCRP)[16,17] and the third showed unique data (1963–1982) from the Mumbai registry,[18] the fourth originates from Kashmir valley.[19]

A summary of latest available data on cervical cancer incidence and mortality rates, including the NCRP cancer registries and the study from Kashmir, is shown in Table 1. Data from the Cancer Atlas are not included since they only provide minimum age-adjusted incidence rates. Age-adjusted mortality rates vary widely across and within states, between 0.2 per 100,000 in Barshi and Dibrugarh District (2005–2006) to 7.7 in Chennai (2004/2005).[8] Age-adjusted incidence rates range from 0.9 per 100,000 in Kashmir Valley (2002–2006)[19] to 22.5 in Aizwal District (2006/2008).[8]

HPV prevalence and type distribution

Twenty-one articles looked at high-risk HPV prevalence or type distribution (Table 2).

Andhra Pradesh and Gujarat HPV prevalence data and type distributions

There is no study on HPV prevalence and HPV type distribution in Gujarat and only one study in Andhra Pradesh (Hyderabad and Medchal Mandal).[15] This study is cited by PATH. The HPV prevalence in healthy and cancer patients was 10.3% and 87.8% respectively. HPV 16 and 18 were the most prevalent types in cancer patients, HPV 52 and 16 were the most commonly found types in the healthy population.

National HPV prevalence data and type distributions

Studies were undertaken in all parts of India.

i) *Regional representation*

Both healthy and cancer patients are equally represented among areas across the country. There are no studies of HPV prevalence in cervical cancer population in north-eastern states. Hr-HPV prevalence in cervical cancer population ranges between 75% and 96.7% between different states.

ii) *Definition of high risk HPV types*

There is no consensus about the definition of high-risk HPV types. Although the IARC defines 13 types as high-risk and five as possible high-risk, some studies define 22 types as high-risk, including for example type 67, 69, 70, and ISO39.[3]

As a result, study design is problematic as some studies look at single phage types while others at multiple types either separately or in groups. For example, some studies displayed the prevalence of each separate type (e.g. HPV16 is 3% and HPV 52 is 1%), while others displayed the prevalence of the combination of types as they occurred in individuals (e.g. HPV16 and 52 is 3%).

Some studies only looked at the prevalence of two types (often HPV16 and 18), others looked at a broad range, sometimes up to 22 types. Four of the twenty-one studies looked only at hr-HPV prevalence without specifying the individual type prevalence.

iii) *Study populations*

The populations under study differed in their health status, age group, location in India (e.g. south, north) and their rural or urban location, making it impossible to compare study findings. For example, some studies included only cancer patients, others only healthy populations, and others mixed populations.

Healthy people have a low hr-HPV prevalence, rates are higher in populations at risk (HIV/AIDS, gynaecological complaints, sex workers), and highest in the cervical cancer population. In the latter group, HPV16 and 18 were most frequently found types. Data on population at risk (for example with HIV/AIDS) or healthy population are not conclusive. Only age is used as a confounder and is adjusted for, while there might be other confounders as for example HIV/AIDS. Only one study looks specifically at HIV/AIDS.

A further bias is that studies may have included mainly the wealthier and urban population with better access to healthcare facilities.

Table 2
High-risk HPV prevalence and HPV type distribution among different Indian populations identified in studies published between 2000–2012

First author, date	*Health Status*	*Age (years)*	*Sample size (persons)*	*Rural/ urban*	*Location*	*Area*	*HPV prevalence*	*HPV types measured in study*	*Top three HPV prevalent types by study*
Aggarwal, 2006 (Indian J Cancer)	Gynaecological complaints	19–75	472	Rural/ urban	Unknown, north India	North	8.2%	16,18,31,33	HPV18 (4%), HPV16 (3.2%), coinfection HPV16/18 (0.4%)
Arora, 2005 (Eur J Obstet Gynecol Reprod Biol)	Healthy	20–60	160	Urban	New Delhi	North	/	16.18	HPV 16 AND 18: (10%)
Basu, 2009 (Asia Pac J Cancer Prevention)	Cancer	Mean 51.4	278	Urban	Kolkata, Delhi, Nagpur, Bangalore	East, north, central, south	/	16,18,31,33, 45,52,53,56, 59,62,67, 69,73	HPV-positives: HPV16 (59.4%), HPV18 (13.3%), HPV33 (4.0%)
Bhatla, 2006 (Int J Gynecol Pathol)	Cancer	25–70	106	Urban	New Delhi	North	/	16,18,26,31, 33,35,39,45, 51,52,53,56, 58,59,66,67, 68,69,70,73, 82,ISO39	HPV-positives: HPV16 (73.6%), HPV18 (14.2%), HPV45 (11.3%) HPV16 and 18, single infection or coinfection found in 83%
Datta, 2010 (Cancer Epidemiol)	Healthy	16–24	1300	Urban	Govindpuri, New Delhi	North	/	16,18,33,35, 39,45,51,52, 53,56,58,59, 66,70	HPV16 (3%), HPV52 (1.2%), HPV51 (0.8%) HPV-positives: HPV16 (37.5%), HPV52 (15.4%), HPV51 (10,5%)
Dutta, 2012 (Int J Gynecol Pathol)	Healthy	25–65	2501	Rural	Rural Kolkata	East	normal cytology 9.9%; abnormal cytology 20.6%; high	16.18	Overall: HPV18 (1.4%), HPV16 (0.6%%) HPV-positives:

(Continued)

Table 2
Continued

First author, date	*Health Status*	*Age (years)*	*Sample size (persons)*	*Rural/ urban*	*Location*	*Area*	*HPV prevalence*	*HPV types measured in study*	*Top three HPV prevalent types by study*
							grade SIL 53.3%		HPV16 (37.5%), HPV52 (15.4%), HPV51 (10,5%)
Franceschi, 2005 (Br J Cancer)	Healthy, cytological abnormality	16–59	1891	Rural	Western Ghats, Dindigul District	South	12.5% overall	16,18,26,31,33, 35,39,45, 51,52,53,56, 58,59,66, 73,82	Healthy: HPV16 (2.8%), HPV56 (1.1%), HPV18,31,33,35 (0.8%) Abnormal: HPV16 (22.8%), HPV56 (10.9%), HPV31 (9.8%)
Gheit, 2009 (Vaccine)	Cancer	28–86, mean 51.4	232	Rural	Sevagram	Central	93.3%	/	/
Gupta, 2008 (Cytopathology)	Minor gynaecological complaints	20–45	769	Urban	New Delhi	North	/	16.18	HPV16 (10.1%), HPV18 (1%) HPV-positives: HPV16/18 coinfection (67%), other HPV types (33%)
Kulkarni, 2011 (Asian Pacific J Cancer Prev)	Cancer	Not stated	60	Urban	Hubli	South	96.7%	16.18	HPV16 (89.66%), HPV18 (86.22)
Laikangbam, 2007 (Int J Gynecol Cancer)	Healthy	14–80	692	Rural/ urban	Manipur, Sikkim, West Bengal	North-east, west	/	16.18	Manipur: HPV18 (2.03%), HPV16 (3.2%) Sikkim: HPV16 (5.06%), HPV18 (0.24%) West Bengal: HPV16 (8.45%), HPV18 (0.92%)

Peedicayil, 2006 (Int J Cancer)	CIN stage and cancer	CIN: average 38.7 cancer: average 48	11 (CIN); 119 (cancer)	Urban	Hospital in south India with patients from South and East	South, east	/	16,18,26,31,33, 35,42,45, 51,53,56,58, 61,62,64, 81,82	CIN-stage: too small sample Cancer: HPV16 (61%), HPV18 (15%), HPV33,35,58 (all 6%)
Pillai, 2010 (Int J Gynecol Cancer)	Cancer	25–87	M 119, N 120, K 85, V 96, B 118, T 129. Total 667	Urban	Mumbai (M), New Delhi (N), Kolkata (K), Vellore (V), Bangalore (B), Thiruvanantha-puram (T)	North, east, south, west	M 89.1% N 91.7% K 96.5% V 95.5% B 91.5% T 89.9% All 92.1%	16,18,26,31, 33,35,45, 51,52,56,58, 59,68,71	M: 16 (72.3%), 18 (5%), 58 (1.7%) N: 16 (68.3%), 18 (12.5%), 45 (2.5%) K: 16 (74,1%), 18 (8.2%), 31 (3.5%) V: 16 (66.7%), 18 (10.4%), 45 (5.2%) B: 16 (69,5%), 18 (5.1%), 45 (4.2%) T: 16 (58.1%), 18 (5.4%), 56 (4.7%)
Sahasrabuddhe, 2008 (PloS One)	HIV	All, median 30	303	Urban	Pune	West	41.7%	/	/
Sankaranarayanan, 2008 (Vaccine)	Healthy and cancer	25–65	review	rural/ urban	Kolkata, Mumbai, Trivandrum, Osmanabad	South, east, wets, central	Healthy: 7.0-10.4%,. Cancer: 75%	/	/
Saranath, 2002 (Gynecol Oncol)	normal, LSIL, HSIL, SCC	not stated	164 (normal), 64 (LSIL), 5 (HSIL), 337 (SCC)	Urban	Mumbai	South	/	16.18	Normal: HPV16 (7%), HPV18 (12%) LSIL: HPV16 (36%),

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Table 2
Continued

First author, date	*Health Status*	*Age (years)*	*Sample size (persons)*	*Rural/ urban*	*Location*	*Area*	*HPV prevalence*	*HPV types measured in study*	*Top three HPV prevalent types by study*
									HPV18 (11%) HSIL: HPV16 (80%), HPV18 (20%) SCC: HPV16 (73%), HPV18 (16%)
Sarkar, 2011 (BMC Infect Dis)	Healthy and HIV positives	Mean: HIV-positives 29, HIV-negatives 30	93 HIV-positives, 1106 HIV-negatives	Rural/ urban	West Bengal	East	Oncogenic HPV types: 46.2% (HIV-positives)	16,18,26,31, 33,35,39,45, 51,52,55,56, 58,59,68, 73,82	HIV-positives: HPV18 (19.4%), HPV18 (7%), coinfection HPV16/18 (7%)
Sarkar, 2008 (J Infect Public Health)	Sex workers	All, starting form 10	229	Rural	West Bengal	East	25%	16.18	HPV16 (10%), HPV18 (7%), coinfection HPV16/18 (7%)
Sauveget, 2011 (Sex Transm Dis)	Healthy	30–59	27192	Rural	Maharashtra state	West	10.3%	/	/
Sowjanya, 2005 (BMC Infect Dis)	Health and cancer	30–65	18 (healthy), 36 (cancer)	Rural/ urban	Hyderabad, Medchal Mandal	South	Healthy: 10.3% cancer: 87.8	16,18,31,33, 35,39,45,51, 52,56,58, 59,68	Community: HPV52 (29.4%), HPV16 (17.6%), HPV58,33 (both 11.7%) Cancer: HPV16 (66.7%), HPV18 (19.4%), HPV33,35,45 (all 5.6%)
Srivastava, 2012 (J Biosci)	Healthy	17–80	2414	Rural/ urban	Varanasi	East	9.9%	16,18,31,33, 35,39,45,51, 56,58,59,67, 68,72,73	HPV-positive: HPV16 (63.7%), HPV31 (6.7%), HPV33 (4.2%)

According to the IARC Monographs3, high-risk or possible high-risk HPV types associated with cervical cancer are 16,18,31,33,35,39,45,51,52,56,58,59 and 68. Types 26,53,66,73 and 82 are possible high risk types.

Discussion

The World Health Organization (WHO) accepts that the baseline epidemiology of the disease should be known and be of sufficient importance to justify prioritizing the intervention, and further, that surveillance systems should be capable of assessing the impact of a vaccine intervention following its introduction.[7] This study shows an absence of epidemiological data in support of HPV vaccine studies by PATH in the two states, let alone any roll out across the rest of India. Recent studies of HPV epidemiology and type distribution show an apparent decrease in cervical cancer incidence (see also AOGIN India Biennial Conference[20]) which must be taken in account.

Limitations of this study are that key papers may have been missed by limiting the search to English language publications between 2000 and 2012, we could not review the quality of the cancer registries in depth.

Cancer surveillance

Cervical cancer surveillance in Gujarat and Andhra Pradesh is incomplete and the data that are available were not used or cited by PATH. An effective surveillance system for HPV vaccine requires that the baseline incidence, prevalence and mortality rates of cervical cancer are established. The cancer registries and the surveillance systems provide an inadequate basis for information because they are not complete or comprehensive in their coverage for every region in India. The effectiveness of an intervention cannot be measured if there is no monitoring or follow-up on epidemiological data. Data for surveillance is critical; if the vaccine is to be rolled out across the country, every subpopulation should be represented equally. The large inter- and intra-state varieties in incidence and mortality rates in India shown by the registries indicate that local data cannot be extrapolated to the national level. The latest NCRP Reports acknowledge this problem in variety for incidence rates.[8]

We could not access all data from all individual cancer registries and some mortality rates or registries were omitted since not all the NCRP registered cancer registries had their data presented in the NCRP Reports. The methods for the GLOBOCAN database are incomplete and difficult to follow. Data are not presented in a standard and consistent manner, so cannot be compared e.g. only absolute cancer numbers or only age-adjusted rates.

We recommend that one comprehensive cancer health information system should be established to give a better oversight of cervical cancer and HPV in India. The NCRP should continue its quality work and expand coverage to include all small registries. The IARC should publish an account of decisions to exclude cancer registries and should align itself with the NCRP.

Cervical cancer incidence and mortality

Contrary to PATHs claims, the overall incidence and mortality of cervical cancer is low, in India compared with other conditions: the highest age-adjusted mortality rate of 7.7 per 100,000[8] compares with an Indian mortality rate of 283 per 100,000 females due to diabetes and cardiovascular diseases[21] and a rate of 26 per 100,000 for tuberculosis (excluding HIV).[22] There are no time trends for cervical cancer in mortality rates available.

Age-adjusted cervical cancer incidence rates of India are low compared to estimates of 50.0 per 100,000 in Zimbabwe and 38.2 in Brazil, Goiania.[8,11] Again, the quality of the surveillance systems and these data are not fully evaluated. Cervical cancer may be a major cause of cancer in females, but cancer registries show that incidence rates are significantly declining (noted between the year 1982 and 2005). This declining trend is also described in other studies.[23,24] There is an absence of data on time trends in mortality rates.

HPV prevalence and type distribution

All five studies performed on cancer patients identify HPV 16 and 18 as most common types. For healthy and at risk populations, there are conflicting findings about which are the most frequent HPV types. Data on HPV prevalence and type distribution epidemiology are incomplete, since inconsistency in study design and different populations make findings difficult to compare and to

extrapolate, even more so because there are varieties in data within and between states.

Recommendations

Cancer registration and surveillance systems should be extended across all population groups, including rural, northern and eastern populations, and vital registry systems should be established for the collection of mortality data.

A comprehensive health information system is required to give a better oversight of cervical cancer and HPV in India, but this would require universal health care and integrated healthcare systems.

Neither the epidemiological evidence nor current cancer surveillence systems justify the general rollout of a HPV vaccination programme either in India or in the two states where PATH was conducting its research. HPV vaccination programmes should only proceed where there is both strong epidemiological evidence and where there are adequate surveillance and monitoring systems.

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