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Fourth decade of Universal Immunization Programme in India: an Introspection

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Abstract: The Universal Immunization Programme in India have been incorporating newer vaccines so that the immunization schedule has been changing rapidly, though varying from one state to another. The number of diseases being protected against has increased from 6 to 14 in the past few years. It should be emphasized that we must ensure all the age appropriate vaccination to each and every child as vaccination is birth right of every child. In spite of almost everyday addressing common people at different levels at different places on different days creating awareness on how provision of immunobiologicals and vaccines by the governmental agencies protect and saves lives of children and, still we are far behind the required immunization coverage in India. It is heartening to know that immunisation program as 'Intensified Mission Indradhanush' re-launched by Government of India in 2017 and supported by UNICEF to vaccinate each and every child reaching the target close to 90% coverage by 2020.

Keywords: Universal immunization programme, coverage, vaccine preventable disease.

Forty years of Universal Immunization Programme

Preamble: Immunization is the most cost effective public health intervention that provides direct and effective protection against preventable morbidity, mortality and disability to a good number of diseases. In early seventies of last century global data showed that less than 5% of infants were immunized against diphtheria, polio, TB, pertussis, measles, tetanus. In India researches on newer vaccine development are not as expected though we are leading producer and exporter of immuno-biologicals.

Globally we are major contributor to decline U5 mortality rate ~ 233 to ~63 (per 1000) in last five decades. Yet in India VPDs still kill over 5 lakh kids annually as we lag behind optimum Routine Immunization (RI) coverage needs improvement with proactive steps. In 2012 the WHO SEA Regional Director raised the slogan 'Call to Intensify RI' and Government of India (GOI): declared 2012 as the year of 'Intensification of RI in India' [1].

History do tell tales: India and China practiced "inoculation" before 16th century. Modern immunization initiated since 19th century lead to research and development (R & D) initiatives in vaccines and beginning in 1890s till date 15 vaccine institutes established in India. World's first plague vaccine by Haffkine (1897) and Manson's development of indigenous cholera vaccine was the most notable achievements of our national institutes. Early research and technological innovation were sidelined as demands for routine vaccine production took priority. India launched its first vaccine BCG in 1962 as a part of National Tuberculosis Control Program. In line with World Health Organization (WHO) Expanded Programme on Immunization (EPI) in 1974 against six diseases to underserved areas, in India initially BCG, DPT (3 doses), Typhoid vaccine was

started in 1978; Oral polio vaccine (OPV) was added next year. In addition to 3 primary doses of DPT & OPV, 2 boosters at 1.5 years and 5 years covered children up to 5 years of age. In 1986 UIP modified policy;

1. To cover 'ALL' eligible children.
2. Immunize 'ALL' pregnant women with TT.
3. Improve service quality.
4. First DPT booster at 2nd year and 2nd booster at 5-year DT (pertussis omitted).
5. Measles vaccine was added at 9 months of age; but typhoid vaccine was omitted from immunization schedule.

In 1988 Indian Government of India (GoI) agreed with Goal of global polio eradication with 192 WHO member nations. In 1995 ambitious project Pulse Polio immunization (PPI) was started for children less than 3 years age in 1997; modified to cover all under five years old children by 2000: House to house component was added to intensify PPI coverage with trivalent vaccine to Monovalent OPV (1) then till date Bivalent OPV (1& 3) in PPI. National Polio Surveillance Project (NPSP) launched in 1997 provided technical and logistic assistance to GoI and working with states to achieve goal of polio eradication. Will all these efforts reported polio cases dropped down from 35000(1994) to 741(2009); last polio case due to wild virus was found on 13th January 2011 in West Bengal in eastern India; WHO: Declared India Polio Free February 25, 2012' [2].

Efforts to augment RI by GoI:

a. For laboratory supported surveillance of Vaccine Preventable Diseases (VPDs), 11 centers across India has been identified with special reference to potential vaccines in collaboration with Indian Council of Medical Research (ICMR).
b. Mother & Child Tracking System: Telephone based tracking of pregnant mothers and children through a web enabled system to make sure all pregnant mothers & children receive full continuum of care including complete vaccination.
c. National Vaccine Policy 2011: GoI provided broad policy guidelines and framework to guide creation of evidence base to justify need of research and development, production, procurement and quality assessment of vaccines under UIP.
d. Efforts are also on to improve health infrastructure in the country: key to optimize the implementation of UIP.
e. NRHM 2005: to re-vitalize primary health care systems including RI to benefit people in difficult, inaccessible & remote areas.
f. Adequate funds: strengthen health system and infrastructure with key focus on Reproductive and Child Health (RCH), including immunization.
g. New safe and effective vaccines against major killers viz. diarrhea and pneumonia were introduced that strengthened UIP [3]

Immunization coverage: Herd immunity in the community protect non-immune population and reduce the risk of outbreak which is achieved when the proportion vaccinated population is at least 90 percent. The percent of at risk or susceptible individuals, or population fully immunized against diseases by immuno-biologicals determines the health of the society. Thus, when immunization coverage is low due to refusal by people or failure of country, citizens as a whole become vulnerable to VPDs.

This ethical dilemma on vaccinations need to be solved by persuasion through government machinery and extensive Behavoiur Change Communications (BCC) to nullify individual liberty and autonomy. Inclusion of a new vaccine in national schedule adds cost of vaccine and logistics to health budget of country. But, it results in savings by reduction of disease burden. So, we must be judicious to introduce new vaccines at expense of existing immunization activity as 'Equity' needs 'TOP PRIORITY' so that vaccine reaches to the section of society who needs it most [4].

Routine Immunization in India: WHO/ UNICEF in 2010 reported Diphtheria-Pertussis-Tetanus (DTP) 3rd dose coverage in South-East (SE) Asia as 77% and in India 61%. During 1985-95 RI coverage has been reported in National Family Health Survey (NFHS I, II, III) showed that coverage of different vaccines in UIP were all low between 15-20% and UNICEF reported nearly similar (15-40%). For Hepatitis B vaccine (HBV) the 3 UIP dose coverage in 16

States/UT was little more (58.9%), yet HBV birth dose is still a challenge in our country. GoI reports showed that there is huge interstate variation in coverages between 12-23 months of ages; whereas in Goa, Sikkim, Punjab and Kerala it is more than 80% Fully Immunized compared to less than 50% in Bihar, Madhya Pradesh (MP), Uttar Pradesh (UP), Nagaland and Arunachal Pradesh.; these latter states with high population burden had 80% unimmunized children; in them 52% of total unimmunized children reside in UP and Bihar. The research group of this article has compiled the published immunization coverage data in Table 1 (NFHS-3, DLHS-3, NFHS-4, Coverage Evaluation Survey (UNICEF 2010).

Table-1: Immunization coverage: UIP six vaccines 12-23-months old

	NFHS-3 (2005-06)	DLHS-3 (2007-08)	NFHS-4 (2015-16)	Coverage Evaluation Survey (UNICEF2010)
BCG	78.1%	86.7%	91.9%	86.9%
Measles	58.8%	69.5%	81.1%	74.1%
OPV	78.2%	66.0%	72.8%	70.4%
DPT-3	55.3%	63.5%	78.4%	71.5%
Immunization coverage				
Full	47.3%	54.1%	62.0%	61%
Partial		34.6%		31.4%
No		11.3%		7.6%

In a recently published study, another interesting finding was highlighted. The immunization schedules of the states of Delhi, Himachal Pradesh, and Haryana were compared among themselves and also with the schedule recommended by the Indian Academy of Paediatrics where some interstate variations were observed. Further, the migrants, service providers, and those users switching between private and public sector many a time are affected due to this variation among the immunization schedules [5]. A study done in Delhi showed that 50.4% 12-23 months old kids were fully and 41.9% partially immunized; 7.6% unimmunized [6].

Barriers to achieve 100% immunization coverage: India is passing through relatively high growth rate with huge population - 27 million born per year making largest global birth cohort. Due to geographical diversity (Hilly with snow bound areas, deserts, tropical forest, remote island territories), cultural diversity (religion, language, tradition, belief, custom) & political instability ("coalition" govts, "politically sensitive areas" are unique and more complex task to achieve full immunization coverage. Moreover, reaching out mobile and migrant population (significant proportion in some states) is another daunting task. Culminating all the above, low immunization pockets are in many states for which special efforts needed to identify and reach. Coverage evaluation survey (CES) from UNICEF showed that reasons for low immunization coverage were Firstly, lack of awareness as they "did not feel the need", "not knowing about need", "not knowing where to go for vaccination" in 28.2%, 26.3%, 10.8% cases respectively. Further, low literacy and adverse effect following immunization (AEFI) even unrelated to a vaccine had negatively impacted health-seeking behavior. There are issues on 'supply side' viz;

1. Inadequate delivery of health services (supply short, vacant staff position, lack training).
2. *Lack:* accountability, inadequate supervision, monitoring.
3. *Lack:* district micro-planning, inter-sectoral coordination, between State and Central governments.

4. Missed opportunities.
5. *Quality assurance:* all reduced coverages. Falsification of data and over-reporting of rates.

Weak surveillance system with lack of diagnostic facility for certain VPDs kept us in dark on disease burden data and low baseline surveillance data to monitor impact of vaccine. "de-linking" of UIP from 'Polio Eradication Initiative' led to deterioration of performance of UIP. Unfortunately, house-to-house rounds of vertical programme activities of PPI made society "dependent" on health workers that adversely affected booth based UIP coverage. Lastly, for resource constraints and competing priorities, we need careful planning and policy-making as fund allocation for RI reduced to $113million in 2011 from $137 million in 2009-10) [7].

Visions to improve immunization coverage we need holistic approach

Political goodwill:

a. "Inter Agency Coordination Committee" needed at National level to increase its focus on routine immunization by Public-private partnership (PPP)**:** GoI, development partner, IAP, IMA, ICDS, Min of Railways, Education, Defence plus inclusion of NGOs with good track records.
b. Ensure and monitor funds release which is not only appropriate but also timely; Uninterrupted supply of immunobiologicals to state level with scientific 'Vaccine stock management system' including 'Inventory control; Central level provide technical support and resources for states to develop evidence based social mobilization plan.

Futuristic IEC planning:

a. Increase demand from users by effective health awareness and bring immunization closer to community by public cooperation.
b. Increase services at fixed sites.
c. Better monitoring and supervision.
d. District authorities made accountable for performance.
e. Efficient immunization service: urban and rural.
f. Periodic mass immunization campaigns for missing kids of regular immunizations.
g. Outreach programs in rural and nomad areas, home visits.

Creative ideas on increasing RI coverage:

a. Increase immunization 'delivery points' in rural and remote areas.
b. 'Immunization booths' at each urban locality viz. slums with accountability of local municipality board members.
c. Optimum mix of manpower e.g. Private Medical Practitioners, Pharmacist, Chemist, retired health care providers etc. for training and re-training including maintenance of cold chain and basic capacity building on vaccines.
d. Full immunization made mandatory for school admission.
e. Incentives in cash/kind to those families' full immunization

Optimum Monitoring:

a. Vaccination is a medical intervention, yet vaccination program like UIP is a management-dominant modality needing managerial, administrative and governance-related inadequacies addressed on priority basis with structured work allocation and monitoring of accountability.
b. Scientific monitoring needed to assess surveillance of VPDs under UIP.
c. To find 'impact' or 'output' of entire vaccination program by disease reduction and demand creation.
d. 2002 WHO, UNICEF call "Reaching Every District" can be recast as "Reaching Every Family".

Operational Surveillance:

a. Create collaborative surveillance system for important childhood infectious diseases with IDSP: state based decentralized surveillance program by MoHFW 2004 with IDsurv-a web-based infectious disease surveillance of Indian Academy of Pediatrics (IAP).
b. *Model:* Active Bacterial Core surveillance, a population-based surveillance system by CDC, Atlanta, US.
c. To compare coverage rates with reduction of prevalence of VPDs covered under UIP.

AEFI Detection, Reporting and Redressal: Functional real-time AEFI and post-marketing surveillance system to allow (and settle) compensation claims for vaccination-related injuries and serious adverse events.

Legal and Ethical Issues:

a. Strengthen regulatory capacity by reliable and visionary national regulatory authority (NRA).
b. Currently Drug Controller General of India is overburdened.
c. Vaccine specific NRA activity needed for licensing, post-marketing surveillance with AEFI surveillance, lot (batch) release process, laboratory support for vaccine testing, GMP regulatory inspections, authorization & ethical approval of trials, etc.
d. Single window system to avoid regulatory delays, and strict guidelines for approval and cancellation of license.

National Vaccine production:

a. Currently 43% of global UIP vaccines come from India: Serum Institute is global leading measles vaccine producer.
b. Increase current liberal support from government-owned institutions like DBT, DST, National Institute of Immunology, National Institute of Virology etc.
c. Need of innovation in public sector units + Public private partnership and share responsibility producing EPI vaccines.
d. Stop 'orphanization' of UIP primary vaccines with declining interest and production by private sector (more interested in newer costly vaccines).

Rescheduling of UIP:

a. Change of 6, 10, 14-week to 2, 4, 6-month schedule.
b. *Rethink:* Polio 'Post-eradication vaccine policy'.
c. Pentavalent vaccine to 6-6-8 vaccines in single shot; Typhoid vaccine: inclusion to be actively considered.
d. 2nd childhood booster of DTP 5 years +*TdaP* at 10 years.
e. *MMR:* Instead of 2nd measles dose through RI campaign, add MR components.
f. Introduce newer vaccines judiciously in cost-effective approach.
g. Currently more than 20 new and improved vaccines are in pipeline.

Horizontal integration:

a. Integrate & converge preventive health services: Vitamin A, deworming, growth monitoring, insecticide-treated bed net.
b. Create synergies and facilitate service delivery to bolster comprehensive disease intervention.

Translational Research:

a. Investment in R&D pay rich dividends: 80 candidate vaccines in late stages trial (30 against major diseases).
b. Better vaccines for existing VPDs, increasing horizon against mass killer diseases viz. *HIV, Malaria, Dengue, RSV, Enteric* pathogens: *E.coli, Klebsiella*, etc.
c. Increase thermostable vaccines.
d. Alternative delivery can be considered for improved compliance by mucosal/oral/ dermal patch/nasal routes.

Immunization specific initiatives:

a. Decentralized planning & need based funding.
b. Improved service delivery through Alternate vaccinators, Alternate Vaccine Delivery and improve services through special immunization drives and better mobilization & tracking through community link workers & vaccinators.
c. Improving supervision & monitoring+ Intensified session monitoring by partnersa and Ongoing training: Only 51% Health Workers trained in national scenario [8].

National Health Policy 2017 (NHP 2017): NHP 2017 directives on immunization intends to reduce the under-five mortalities to 23, neonatal mortality to 16 and still birth to single digit numbers. The policy ensures complete immunization for more than 90 percent of newborns [9].

Mission Indradhanush: Since 1985, full immunization coverage could not surpass 65% despite all efforts. Immunization coverage slowed down in the new millennium with merely 1% increase per year during 2009-2013. Mission Indradhanush focused on

interventions, for full immunization coverage to more than 90% children under UIP, launched in December 2014 stressing on low coverage areas/pockets with a special drive for all missed cases among target of 2.47 crore children and around 67 lakh pregnant women per year. Intensified RI campaigns was targeted through special catch-up campaigns to rapidly increase full routine immunization coverage through collaborative process involving major stakeholders by implementation of learnings from polio eradication programme.

Further, strengthening monitoring and evaluation mechanism contribute to health systems support - identify and enlist unvaccinated & partially vaccinated beneficiaries, track and vaccinate through four campaigns every year executed at National, State, District, Block/Urban levels [10].

Intensified Mission Indradhanush: States conducted drives for 7 working days from 7th of every month since 7th October 2017 for four consecutive months excluding Sundays, holidays & RI days. Increased focus on convergence with other ministries/departments on MCH, PRIs, Urban development, Youth affairs, NCC etc. with ASHA, ANMs, AWWs, under NULM, SHGs crucial for successful implementation. Increase focus on urban areas: Focus gaps and map underserved urban population + need-based deployment of ANMs for providing vaccination. Mobility support to field staff for deployment to such areas in urban as well as rural areas will be provided.

Main lacunae of coverage: False reporting- due to absence of monitoring; Missed areas where newborn missed with poor newborn tracking; Encouraging fixed-day and fixed-site session based approach with improved quality control of service to reduce trained manpower dropout; Poor team concept in our 3-tier health care delivery system; Missed children in High risk and remote areas (c.f. Migrant); Unusable stage vials of immuno-biologicals; Augmenting AEFI surveillance (reporting & management); Optimizing cold-chain space & efficient vaccine stock management practice at various levels (state/district/block) plus enforcing injection safety and BMW practice (c.f. guidelines) [11-12].

Research aspects of immunization: the missing link

Human immune system is composed of dedicated cells and tissues interwoven via cytokines and dedicated for the outcome of specific defensive responses from dynamic and functional webs linking thousands of components. Vaccine delivery options changes differing geographically based on immunobiological information among five main types: Live attenuated, Inactivated,- Subunit, Conjugate vaccines and Toxoid [13].

A holistic insight of the different parts of the immune system helped us to understand the mechanisms of responses and to predict vaccine efficacy in different populations well in advance. The integration of the human immune response and systems biology approach applied to infection and vaccination improves our basic knowledge of dysregulations of immune system enabling future translational research. Newer research techniques like microarray and RNA sequencing to note the immune response: flow cytometry, flow Cytometry by time-of-flight (CyTOF) for different immunoglobulin study; Next Generation Sequencing for T-cell receptor study; Antibody profile by Protein microarrays, Peptide microarrays, Cytokines and Chemokines for cellular metabolic states predictive outcome armed us to epitomize immunology [14].

DNA vaccines are new types of sub-unit vaccines, transfects in vivo cells by DNA plasmid resulting in an immune response. DNA vaccines delivery into living cells leads to expression of protein of interest in vivo with effective induction of both humoral and cellular immunity. Plasmid, a circular double stranded DNA molecule contains genes encoding one or more proteins of a pathogen. Recombinant plasmid can be generated by using recombinant DNA techniques, which is non-infectious, non-replicating and encodes only the antigen of interest as compared to live attenuated vaccines or viral carrier systems. It induces both cell-mediated and humoral immunity responsible for improved performance of the vaccine. Immunization by DNA vaccines decreases frequency of child doses and suits in immunocompromised hosts.

DNA vaccines are stable, easy to freeze dry and reconstitution and can be manufactured inexpensively in large quantities in pure form. Limitations of DNA vaccines are that they cannot substitute for polysaccharide subunit vaccine.

In spite of extensive and elaborative research pertaining to DNA vaccine, there are certain key areas viz. amount of plasmid DNA to be administered, delivery specification to appropriate antigen presenting cells, antigen expression by DNA vaccines, number of boosters needed and optimum time interval between boosters. The major challenge in this field of research is to establish the clinical utility of DNA vaccines for optimum benefit of mankind [15].

Further, since last eighty years we know that certain components of microbes like double stranded RNA, lipopolysccharide, make good adjuvants though the biochemical basis of their action less understood. Adjuvants help the immune process by co-stimulation when the vaccine is given by inducing the synthesis of type I interferons, activate macrophages and other cells of the innate immune system, and this activation prime T and B cells of the adaptive immune system. They appear to be the molecular "bridge" between innate immunity and adaptive immunity. Adjuvants bind to receptors on the macrophages, and this binding kicks Trif into action which causes maturation of the macrophages by release type-1 interferons.

These type-1 interferons cause paracrine or the autocrine activation. In either case, the activated macrophages then begin to express essential "costimulatory" molecules like CD80, CD86, and CD40 that finally activate T-cells of the adaptive immune system, and the active T cells produce a highly specific immune response against the invader [16]. Moreover, an Oxford University based initiative with reductionist approach is evolving a molecular superglue that can facilitate the rapid development of robust and novel vaccines targeting a range of diseases. Discovered in 1963, virus-like particles (VLPs) have become a cornerstone of a number of vaccines. Resembling viruses but without pathogenic material, VLPs can instead be coated with bug-busting antigens to efficiently be combined with number of antigens to produce stable vaccines that induce robust antibody responses [17].

Risk of under protection

We have eradicated small pox, and polio and substantial reduction in the incidence of many VPDs. Progress in last two decades slower: Introduction of newer antigens in UIP, National Vaccine Policy, & acknowledge the need to intensify RI are steps in right direction. We have to remove impediments with motivated stakeholders in politics and bureaucracy, with public policy advocacy and optimize immunization with shift of objectives from 'targeted approach' to 'holistic approach.

Print and electronic media need extensive coverage regarding need of immunisation to children who are most vulnerable to life threatening infectious diseases like pneumonia and diarrhoea which are leading causes of death in children in India that are preventable by proper immunization coverages [18-19]. Further, multiple agencies conduct immunization in rural and urban areas that need to be converged with optimum utilization of manpower as per NHM. [20].

Community participation and convergence of services

Bihar had launched MUSKAN model with following plans of actions: Coverage based Incentive: Tracking newborns through due list and performance based monetary incentive led to coverage 80% per month; Local women' s group meeting conducted twice a month and thus creating awareness on Health, Nutrition and Vaccine; Supportive Supervision in Integrated approach supervised by MO+ICDS official with Random verification and cross-check of beneficiaries with monetary incentive basis to link workers; Funding support received from GOI under NRHM that increased for RI twice in last two years; Regular Review was done at all levels and monitor by state/partners holds the key to bridge gaps [21]. Further, traditional healers, the untapped potential and who are innovatively and optimally utilized in the community based medical care in many countries of the world including palliative care, can be creatively utilised in increasing the immunization coverage [22].

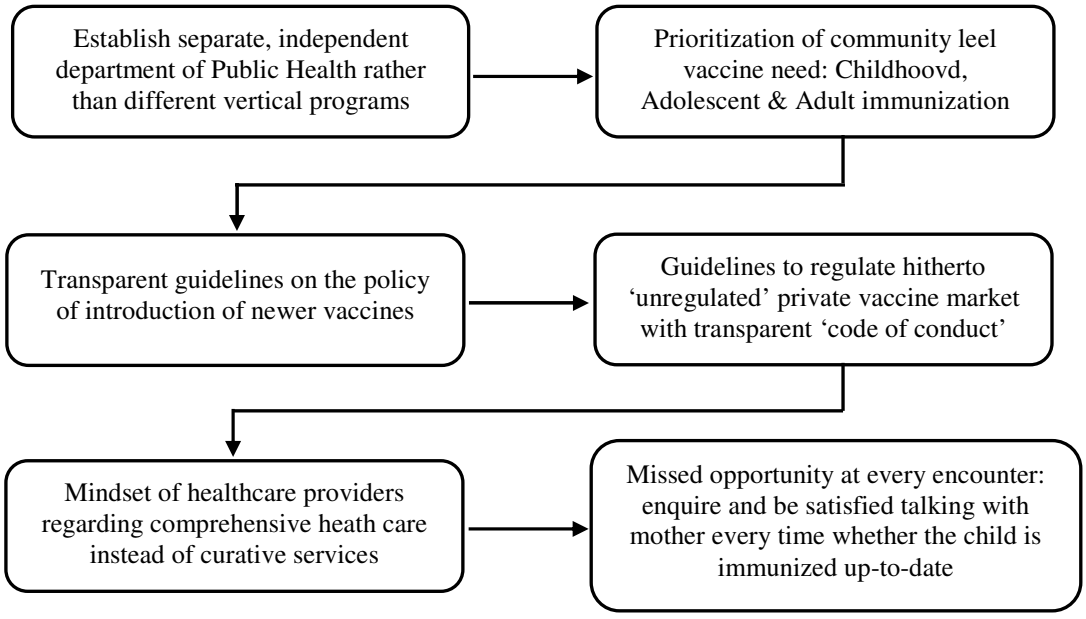
Perception of stakeholders

Some people argue that naturally acquired immunity - immunity from having the disease itself is better than the immunity provided by vaccines. However, natural infections can cause severe complications and be deadly. This is true even for diseases that most people consider mild, like chickenpox. It is impossible to predict who will get serious infections that may lead to hospitalization. Vaccines, like any medication, can cause side effects. The most common side effects are mild. However, many vaccine-preventable disease symptoms can be serious, or even deadly. Although many of these diseases are rare in this country, they do circulate around the world and can be brought into the U.S., putting unvaccinated children at risk. Even with advances in health care, the diseases that vaccines prevent can still be very serious - and vaccination is the best way to prevent them [13]. In a recent study by Indian researchers on the perception of doctors in India for immunization coverage of their own children**,** it was unfortunately noted that complete immunization till date even for the UIP vaccines was nothing better when compared with the national statistics. It is also likely that at times doctors are unaware of the newer and additional vaccines and their importance in vaccination schedule (presuming cost is not a limiting factor for them) [23].

Cancer and vaccine preventable diseases

Many malignancy, cardiovascular disorders, neuropsychiatric disorders and other chronic diseases are caused by VPDs. So with optimum coverages of VPDs we can redusce burden of so called 'non-communicable disease' [24]. Critics of immunization argue that reductions in infectious disease happened as the result of improved water supply and sanitation (not only immunization), or these diseases were in declining curve. These issues are short of scientific truth as the incidence of VPDs were fluctuating and dropped to near zero till specific vaccines were put to practice [25]. Other researchers argued that the immunity granted by vaccines is only temporary and requires boosters, whereas those who survive the disease become permanently immune [26].

Take home message: 'Lip service' versus 'Heartfelt service' [27]



Conclusion

Immunization delivers excellent results in reducing morbidity and mortality from childhood infections. With a human face we need to achieve coverages leading to drastic reduction in infant and children morbidity, mortality and disability in our country.

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