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Title: "PERSPECTIVE: CONVENTIONAL INFECTION PREVENTION AND CONTROL PRACTICES IN POST-ANTIBIOTIC ERA"

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Abstract:

The antibiotic or antimicrobial resistance is rapidly spreading in microbes relevant to human health. Two visible major contributory factors have been the indiscriminate overuse of antimicrobials for preventing diseases in human and to enhance the productivity in agriculture sector. To mitigate the potential threat posed by post-antibiotic era, the global health stakeholders have been making extra efforts at a war footing to formulate and implement global and national plans of action. In the current article, an endeavour is made to provide a perspective to look beyond the current focus on just use of the antimicrobials. Attention has been drawn towards various obvious and not-so-obvious self-preservation infection-prevention practices in vogue from the pre-antibiotic era whose usage has been on decline in the antibiotic era for various reasons. Particularly, the practices with a clear potential to effectively decrease the spread of pathogens through contact, curtail the evolution and dissemination of the antimicrobial resistance in local environment and its introduction into the global community, should be Identified and strengthened to make them part of comprehensive hygiene and quarantine practices. Broadly, the suggestions pertaining to the personal and community hygiene including bereavement practices, isolation and quarantine of suspected pathogen carriers, and water and environment security have been made to invoke a constructive debate and discussion among various stakeholders for their evaluation and implementation to effectively delay the development of antimicrobial resistance wherever possible and disrupt its spread to pathogens.

1.1 Introduction/ The Problem

The antimicrobial resistance is being reported from an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi from all over the world. It is posing an ever increasing grave threat to the global public health [1-3]. Its emergence is primarily ascribed to indiscriminate use of antimicrobials to prevent disease occurrence in human and to enhance the productivity of agriculture sector [2,3]. Resistance to the introduced antibiotics or antimicrobials are emerging in pathogens and spreading worldwide at an ever increasing rate. If an effective strategy to stem the antimicrobial resistance spread or containment could not be found or put in place soon, it may void all the gains made by us in controlling common microbial diseases in the last century [3-6] and may have the capacity to hurl us back into the dark ages of pre-antibiotic era when current form of antibiotics or antimicrobials were not available. The control and effective containment of antimicrobial resistance spread would require both action and support from all sections, *i.e.,* inter-government bodies, state governments and all sections of the society, both as a group as well as individual entities.

The precariousness of the current situation can be gauzed from the recent statement from World Health Organization (WHO) on antimicrobial resistance that states 'WHO's 2014 report on global surveillance of antimicrobial resistance revealed that antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals' [3]. A large proportion of common bacterial infections (*e.g.,* urinary tract infections, pneumonia, bloodstream infections) which were earlier amenable to common antibiotics are showing resistance to antibiotic treatments [7]. Recent surges in the cases of supposed hospital-acquired infections of highly methicillin-resistant *Staphylococcus aureus* (MRSA) strains as well as those of different multidrug-resistant Gram-negative bacterium are posing a big challenge to our ability to treat them. Tuberculosis - a scourge since biblical times, which had remained at bay for some time during the last century with the introduction of antibiotics, has again started raising its head in the form of multidrug and extensively drug-resistant tuberculosis. The number of new cases of multidrug-resistant tuberculosis (MDR-TB) being reported is continuously increasing. It had touched the mark of 480,000 new cases in 2013 in addition to the continuously increasing number of the extensively drug-resistant tuberculosis (XDR-TB) being reported from >100 countries which would require more extensive treatment regimens for its effective control or treatment. The resistance of Malaria pathogen to the last line of defence drugs (*e.g.,* Artemisinin combined therapy or ACT) though initially reported in Cambodia is now being documented all over the surrounding Greater Mekong region countries as well as other places [8]. The emergence of antibiotic resistance is continuously increasing. Without the urgent coordinated action, the world would head towards a post-antimicrobial era, in which common infections and minor injuries, which have been treatable for decades, can once again kill [7]. The situation warrants immediate and concrete steps from all quarters including the world bodies [4,5], state governments [6], society and most importantly the individuals. The threat cannot be just averted by the concerted efforts of a few institutions rather all-encompassing comprehensive national and international plans needs to be put in place with more focus placed on individuals and local community practices.

1.2 Suggested Global Roadmap from WHO

Sensing the urgency to combat the global emergence of antimicrobial resistance, the World Health Organization (WHO) brought out a comprehensive policy document to combat antimicrobial resistance as early as in year 2011 that places major stress on following six broad guiding principles [9]

1. Commit to a comprehensive, financed national plan with accountability and civil society engagement

2. Strengthen surveillance and laboratory capacity

3. Ensure uninterrupted access to essential medicines of assured quality

4. Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care

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5. Enhance infection prevention and control (IPC)

6. Foster innovations and research and development for new tools

Though all points need support and promotion from state or world bodies to control the antimicrobial resistance emergence or spread, an individual's role and overall contribution as a part of society may be further boosted through education, awareness programs and training to meet the aims of points 4 and 5 to prevent or delay the progress of ensuing onslaught of antimicrobial resistance. For stemming the spread of antimicrobial resistance in pathogens proper usage of antibiotics or antimicrobial and their proper disposal is highly recommended. For infection prevention and control, the policy document explicitly encourages the hand hygiene, patient placement barrier precautions, aseptic practices, appropriate antimicrobial usage, sterilization and disinfection, environmental hygiene and waste management and facility environmental design for appropriate infection prevention and control (IPC) practices. WHO also stresses the need to have the practices be adaptive and suitable based upon the local environs or needs. It is up to the local government and society to formulate and implement appropriate measures through education and support to achieve the stated objectives. Considering the urgency of the antimicrobial resistance spread, in May 2015, World Health Assembly (WHO) adopted a global action plan with first three objectives, namely, `improve awareness and understanding of antimicrobial resistance through effective communication, education and training; strengthen the knowledge and evidence base through surveillance and research; reducing the incidence of infection through effective sanitation, hygiene and infection prevention measures' stressing the same [10]. For the successful implementation of a strategy being promoted for implementation/adoption by individuals or group of individuals to curtail the spread of antimicrobial resistance spread, it needs to be effective, applicable, as well as amenable to local environment and beliefs of the population so that it may be taken up or brought into the practice easily.

2. Perspective: *How to control infection?*

'*Act locally to solve globally*' may have to be made one of the cornerstones of any future strategy to solve the global problem of the emergence and spread of antibiotic or antimicrobial resistance in pathogens. Current post-antibiotic era could be considered akin to the time in history when antibiotic or antimicrobials were not available. Most of the current hygiene and community practices are remnants of the established customs and practices followed by the societies of the past when current form of antimicrobial agents were not available to prevent and control the spread of pathogens or diseases as well as secure and protect the environs. Many such practices are in disuse in the society at large due to a variety of reasons including but not limited to the general lack of awareness in public to the logic behind those practices. Some of them which seem to be becoming relevant again in the context of post-antibiotic era are discussed below.

2.1 *Restricted contact with possible pathogen carriers:*

The avoidance of or quarantine of the suspected pathogen carriers is a widely used practice. In the past, strangers or people coming from other areas based upon the closeness to native population were used to be kept separate in dedicated visitors place something akin to modern day guest houses. For example, not long ago, customarily the marriage parties in the village communities (e.g., Indian subcontinent) were used to be camped outside and away from the living quarters of the village settlement usually at a dedicated place, such as orchards outside village that would also have its own dedicated water supply from wells. The interactions between resident population and outsiders were made to be distanced and measured for a definite time period. This would have possibly allowed prevention of the spread of new pathogens to new population and its timely detection in case the travellers have acquired it even during their journey. Although difficult to follow as such in current scenarios or in cities, something akin to it may be followed during disturbances, natural or manmade disasters when a population may have to migrate or needs to stay at different places temporarily. Currently, the camps usually built up in these situations can be regarded as a useful extension of those age old practices. However, the general awareness of the both native and non-native populations about the benefits of the measured intermingling practices needs to be increased to get their key support in its compliance. It would be necessary to reap the benefits of such practices in terms of curtailing the spread of antimicrobial resistance in pathogens as we go further in the post-antibiotic era.

2.2 Observing Mourning Practices:

The mourning practices in vogue need a fresh look on their possible benefit as an infection control strategy. Different societies have been following mourning practices with variable days of strict mourning that we may refer as 'quarantine-mourning' when immediate family members mostly stay home for 3 to 12 days and a period of 'restrictive-mourning' when only restrictive intermingling of the family members of the deceased among themselves and with other members of the community is allowed for a definite period that ranges from few days to years. Besides the obvious psychological significance of these mourning practices to the bereaved family, the possible community health perspective has been largely overlooked in the antibiotics era. The potential benefit of the 'quarantine-mourning' practice as an infection control measure becomes clearer from a look at the incubation period of some of the deadly communicable diseases with higher case fatality rates (see Table 1) that would have been present in different communities at different points of time in pre-antibiotic era. The incubation time for most of the deadly diseases is coincidently usually less than 3 days to upto 10 days, close to the number of days the 'quarantine-mourning' is observed in different cultures. During 'quarantine-mourning' in different cultures usually all mourners who have attended the funeral or took part in a funeral procession are supposed to cleanse themselves, *e.g.,* wash their hands, feet to take bath before coming back to households. In this period, the general population or neighbours may visit the house of deceased to show respect their contacts with the family members of the deceased are restricted. Additionally, the visitors before leaving and when they reach their households before interacting with others, are usually supposed to perform different levels of self-cleansing. Bereaved family members on the other hand are supposed to not attend or avoid public gathering, rather remain confined to their house - effectively curtailing the chance spread of pathogens that the deceased may have passed on to the them. For example, in the Indian subcontinent, among the mourners family the person who has performed last rites, who is usually the eldest son that may have in all probability tended to and have come in longer contact with the deceased parent or the spouse, remains untouchable even to the family members and sleeps in a separate quarter (in a solitary confinement, an effective quarantine strategy) within the family for a period that extends upto 12 days. A general time course of the immune response [(both primary (priming) and secondary (protective)] in a healthy host is shown in Fig.1. Considering the general time course of a secondary protective immune response against any pathogen to which a host is primed, the mourning period would be enough for the host's (mourner) secondary immune response to kick in (takes <3-4 days to rarely upto 10 days) and eliminate any residual pathogen acquired from the deceased during tending. Alternatively, it would provide sufficient incubation period (see Table 1) for a deadly communicable pathogen that would have been the reason for the death of the individual, to show up in the unprimed mourner host – essentially protecting the community at large from any deadly infection. So such isolation and confinement strategies may have had developed based upon the observation in pre-antibiotic era to increase the chances of the survival of a population and at the same time stem the spread of any potential deadly pathogen or any new incurable disease to which treatment options might be limited. Similar practices in all cultures with clear potential to control or prevent the spread of pathogens need to be identified and promoted.

Small children and females are given special treatment in customary bereavement proceedings. Unless absolutely necessary, they are consciously kept separate from the proceedings that may involve coming near to the deceased. These facts can be better understood in terms of decreasing the chance of acquiring infection and its transmission. The fact about small children is understandable given the immunity status of children which makes them relatively prone to a number of acute diseases with deadly consequences. Females being the keel of a family and major social contact point to the community, any chance infection could rapidly spread to other members of her family as well as to the community. Keeping these infections at bay by implementing customary checks in place, earlier civilizations possibly prospered even in the absence of current form of antimicrobials. *Current situation, where we are inching towards post-antibiotic or post-antimicrobial era which would be akin to pre-antibiotic era where our access to effective antibiotics or antimicrobials would be limited, warrants serious rethinking about our current hygiene and* *infection control practices and at the same time requires re-evaluation of the usage of the old customary practices in the current scenario.* The useful practices may be readapted to the requirement of modern times to contain the spread or infection by pathogens in the post-antimicrobial era.

2.3 *Prevent tracking of the pathogens and their introduction into new environs or food products*:

Any set of practices that may check the spread or introduction of pathogens in new environs or food products could help slow down our march in post-antibiotic era. One of the prominent characteristic of the established societies of the past had been the tremendous stress placed on practices that seemed to effectively decrease the potential pathogen load in the place of living through cleanliness principle. Attention to some of the dying conventional practices that may be helpful in the current scenario is being drawn. The convention of keeping the street shoes/footwear outside of primary dwelling area, washing of hands and feet before entering in any house, use of footwear dedicated to the place (or not at all) is one of the most observed practise still today. The movement of people not involved in cooking in and around kitchen area is generally restricted and those directly involved usually cleanse themselves before starting afresh. Somewhat similar practice that may sanitise the surface around cooking area and prevent contamination of the prepared food and ensure its safer upkeep can be promoted through awareness campaigns. Keeping the street footwear away from the place where food produce is processed (*e.g.,* chaffing of wheat, rice) is another common practice that is still followed, although with diminished vigour, in the villages of the Indian subcontinent. Usually, a person is supposed to go there after cleansing themselves such as after taking bath or atleast having his hands and feet washed. In case footwear is necessary, dedicated footwear that is usually kept separate for the purpose is used for that particular purpose. *Based upon our current understanding of pathogen transmission, the use of space specific/dedicated clothing and footwear, hand and feet hygiene, restricting entry or contact with suspected pathogen carriers may be suggested and promoted through educational awareness campaigns.* However, the potential merit of the conventional practices in preventing spread of pathogens needs to be evaluated, and if found suitable may be widely publicized and if required adapted to different independent scenarios.

2.4 *Securing water supply:*

Water is a primary requirement for any society for sustenance but it doubles up as a primary source of infection if the water supply is contaminated. The WHO has time and again stressed the need of the prevention of contamination of drinking surface water to prevent disease spread and outbreaks [11]. Not in very distant past, to have water security one of the prominent feature of the human settlements had been the presence and the active maintenance of 'sacred' water reservoirs whose water could be used for human consumption along with the maintenance of bigger lakes/ponds outside the settlement in the catchment area to avoid rainwater flooding and at the same time allowing efficient rainwater harvesting and water storage. Any disposal of waste contaminated material in those water bodies was forbidden. At the local level, the maintenance and use of such reservoirs has been in disuse and have been degenerating for last half a century or so due to apathy of populace and administration because of the temporary loss of their usefulness and our ignorance of their supposed purpose as a result of different contributing factors such as the advent of piped water supply, progressive increase in the availability of antibiotics/ antimicrobials, change in the administrative setups with increasingly more dependence on a larger organized city or states.

The direct discharge of sewage that included human excreta in waterways/rivers primarily started in a big way in Middle Ages [12] which slowly grew to a worldwide practice. Later due to increased load of population led to the development of sewage disposal systems to get rid of the 'stink' that engulfed big cities situated on the banks of rivers. It still remains an unfulfilled dream to not contaminate the water except in certain well developed cities of the West [11]. Additionally, the endeavour to connect all surface runoff through emergency drainage systems to avoid flooding in local catchment areas has led to creation of an all-encompassing giant drainage system which has led to the development of a conduit to contaminate the whole earth rather than keeping it local. Though this development of drainage system appears to temporarily solve the local problems of flooding in closely located settlements and helps with even distribution of water to larger area, it is leading to slow and painful deterioration of the ecosystem as a whole. It is, in all probability, helping the dissemination of the newly emerged pathogens, their acquired antibiotic or antimicrobial resistance and pathogenicity, which could have been contained locally, to slowly become global scourge. *There is an urgent need to evaluate and rectify the design of the existing drainage systems to effectively breakup or dismantle the all-encompassing giant drainage systems covering large areas that have developed over the years or are also currently being built in other parts of the so called under-developed world so that we may contain and preserve our local environs and at the same time decrease the possibility of the coevolution of pathogen, their acquisition of antimicrobial resistance and the chance of dissemination of any newly emerged pathogen to the global community*.

2.5 *Preventing spread of pathogens through drinking water and contact surfaces:*

As per WHO, the prevention of spread of pathogens through drinking water still remains a big challenge in the third world countries for a variety of reasons [7]. Any practice that may help curb the spread of antimicrobial resistance and the pathogens should be encouraged. Boiling of water along with the use of different kind of filters to remove contaminants and various pathogens remains a common practice in areas known for questionable water quality. The areas where it is not a recognized problem may also benefit from such practices or contraptions as it would effectively decrease the overall chance of the spread of pathogens in a community. Additionally, the use of antimicrobial surfaces in relatively crowded areas could be further promoted to help mitigate the problem. In the past, copper had been used as such or in the form of various alloys to make pots/ utensils for storage and serving of water. Copper and its various alloys (brass, bronze, cupronickel, copper-nickel-zinc etc.) have been demonstrated to be natural antimicrobial materials with natural 'touch surfaces' that kill various pathogens, *e.g.,* nosocomial bacterial pathogens [13-14], coliforms [15,16], viruses [17], that pose threat to public health in general, by coming in their contact. It has been shown that bacterial pathogens in water do not survive if they have been kept in a copper vessel. Copper ducts/tubing with their antimicrobial 'touch surfaces' are currently employed in many modern air conditioners and water pipes to decrease the overall microbial load. *It is advisable at this* *juncture to encourage the use of copper alloy door handles, water tap fitting, water cooler taps, water containers for drinking water, and copper ducts for fitting at dwelling units.* However, the use of copper in drinking water pipes, utensils and vessels may be only promoted in area with known non-corrosive water or precaution must be taken to not overdose ourselves with copper resulting in copper toxicity [18]. *The use of copper touch surfaces may be extended to hospitals where the pathogen loads are high (e.g., wash basins, door knobs, etc.).*

2.6 *Redesigning of commodes/urinals:*

The commodes/urinals may be another important relatively neglected source of the spread of antimicrobial resistance/ pathogens to unsuspecting population. The current design of commodes and urinals needs a rethink to especially contain the spread of enteric and urogenital pathogens. The redesign needs to ensure lesser aerosol generation and contamination of the surrounding area as well as the person (*e.g.,* larger slanting angle, drier catchment area, increased depth of catchment area). The use of antimicrobial contact surface would further enhance its utility. A drier design with inbuilt mechanism to suck in the excreta something akin to that is currently used in aeroplanes is required atleast in public convenience places. It would help in slowing down the spread of anti-microbial resistance and enteric pathogens atleast in relatively lower population density areas.

2.7 *Adhering to 'Hand and Footwear Hygiene'*:

The WHO's 'SAVE LIVES: Clean Your Hands' campaign highlights the importance of hand hygiene in health care and to 'bring people together' in support of hand hygiene improvement globally [19]. There is no denying that hand hygiene is the most important contributor to the spread of pathogens in health care setting. However, *besides stressing on adherence to the principle of hand hygiene in all settings for preventing common enteric and skin diseases it should also include the largely ignored hygiene of the feet/footwear to control the tracking of pathogens to new environs or unsuspecting individuals which will become more and more important with each passing day as we move further in the post-antibiotic/antimicrobial* era. We may even be able to slow down or even halt our collective march in post-antibiotic era if we take the necessary steps now. The WHO body may need to highlight this issue - making it a part of its global campaign. Additionally, the potential of one lesser talked practice of eating meals together in various social or religious gathering, as a means of spreading antibiotic resistance or pathogens needs to be seriously evaluated. The possible safer limits of eating together in community gatherings needs to be worked out and masses may need to be sensitized about the findings. Although, specific examples where a footwear had been identified or shown as a source of infection/ pathogen may be not heard of except in the hospital settings due to a variety of reasons, the examples of illness acquired from eating together in a community gathering are rather commonplace. We need to come up with general guidelines for such gatherings and promote the practices that may be able to curb the spread of pathogens in such settings.

2.8 *Changing practices to separate isolate and quarantine possible source of acute infection:*

As WHO rightly puts 'the source of acute infections is more likely to be the survivors, human remains only pose health risks in a few special cases requiring specific precautions, such as deaths from cholera or haemorrhagic fevers' [20]. *The separation, isolation and effective quarantine of the possible pathogen carriers who have come in close contact with a deceased individual who may have died of a communicable disease needs to be strengthened.* Most of the deadly, communicable disease have a mean incubation period of 1-3 days to <10 days (See Table 1). Consider, a death occurs in a family but the cause remains nondescript or undiagnosed as a result of pathogen acquiring more pathogenicity or a characteristic that was previously unrecognised or not known for a disease, there always remains a chance that the bereaved family may spread it to others in the community unknowingly, if they interact with community at large. The practice of mourning the death and the supposed 'quarantine mourning' practices in place to decrease the contact with bereaved family members especially the dearest one who would have tended the deceased has varied from 3 to 12 days in different cultures as discussed above in section 2.2. Current practice of allowing upto 3 days leave from work to mourn the deaths may be sufficient to stem the spread of deadlier diseases but may not suffice to contain the milder ones. So the allowed leave from work for the bereavement may be enhanced or longer leave may be encouraged as a matter of policy. It can be even made mandatory to have longer leave period such as 10-14 days in cases where the person had closer contact/ association with the deceased such as lived with him to allow the timely detection of pathogen carrier bereaved before he becomes the source of infection to other members of the society. Additionally the custom of not taking part in bigger gathering whether celebratory or bereavement and the customary ban on marriage for a year or so may be viewed as 'the watch period' by design to contain the spread and at the same time allow timely detection of the acquired longer incubation period requiring chronic diseases. The state players and WHO being the nodal point of all such global efforts may also consider these facts in formulating their policies about health and wellbeing of the global society.

3. Concluding remark

The motto to contain the spread of antimicrobial resistance at current juncture can be summarised as '*Beseech verity; berate headless'*. *We must seek for and actively work towards the development of practices, procedures and contraptions that may stem the spread of antimicrobial resistance and the pathogens.* The post-antibiotic or post-antimicrobial era can be considered akin to the time before the discovery of antimicrobials/ antibiotic where our survival as a species was dependent upon as well as the result of our collective effort to keep the pathogens at bay and prevent spread of pathogens at all cost. It was done through the collective promotion and following such practices that effectively curtailed or eliminated the spread of pathogens from unknown sources through personal, family and community hygiene practices while that from a suspected source through mandatory quarantine and evaluate practices under the guise of various customs. *The customary pre-antibiotic era practices may be evaluated for their potential benefit in current scenario and if found suitable may be promoted, tailored or reinvented to the need of the occasion*. To curtail the spread of pathogen, we would need to put practices in place that may effectively prevent the spread at the interfaces/ boundaries, something as done by surgeons at the time of entry or exit to the operation theatre. For example, we may strengthen the practice of changing to dedicated space-specific clothing (*i.e.,* 'gowns' and 'footwear') akin to 'personal protective equipment' of a surgeon whenever moving from one space to another, such as that from home to outside or *vice versa*, and promote conscious personal cleansing/hygiene practices (*e.g.,* washing of hands and feet or taking a shower) at the interfaces.

In places of bigger gatherings with increased potential to spread or acquire pathogens we would need to increase the personal protection through engineering feats that would provide lesser chances of pathogen spread, *e.g.,* personal hand and footwear sanitization upon entry and during exit, spread-out sitting spaces in waiting or holding areas with sufficiently controlled air flow to decrease the chances of pathogen spread through aerosols, decontamination of the air leaving individual hospital buildings, redesign of restroom urinals/commodes to decrease aerosol generation during use and controlled airflow to prevent transmission of aerosols among its users, separate restrooms for patients on antibiotics/antimicrobials, separate collection and incineration of wastes generated in hospitals including sewage at all costs. No chance should be spared to disallow the spread of pathogens in the environs. In the foreseeable future, we may have to make additional separate sewage collection systems available for the collection of antibiotic or antimicrobial contaminated materials and incinerate the dried waste material or come up with other ingenious catalytic ways to have the polluting antimicrobials degraded into harmless compounds before their disposal into general drainage system to control the antimicrobial resistance development and spread. In current scenario of surging antimicrobial resistance we need to find ways to contain it through breaking the chain of transmission and spread of microbes by adopting practices that may help us achieving so. A greater degree of coordination and understanding as well as thorough discussion among various stake holders is urgently required to devise plans to effectively contain the spread of the antibiotic or antimicrobial resistance before it becomes too late.

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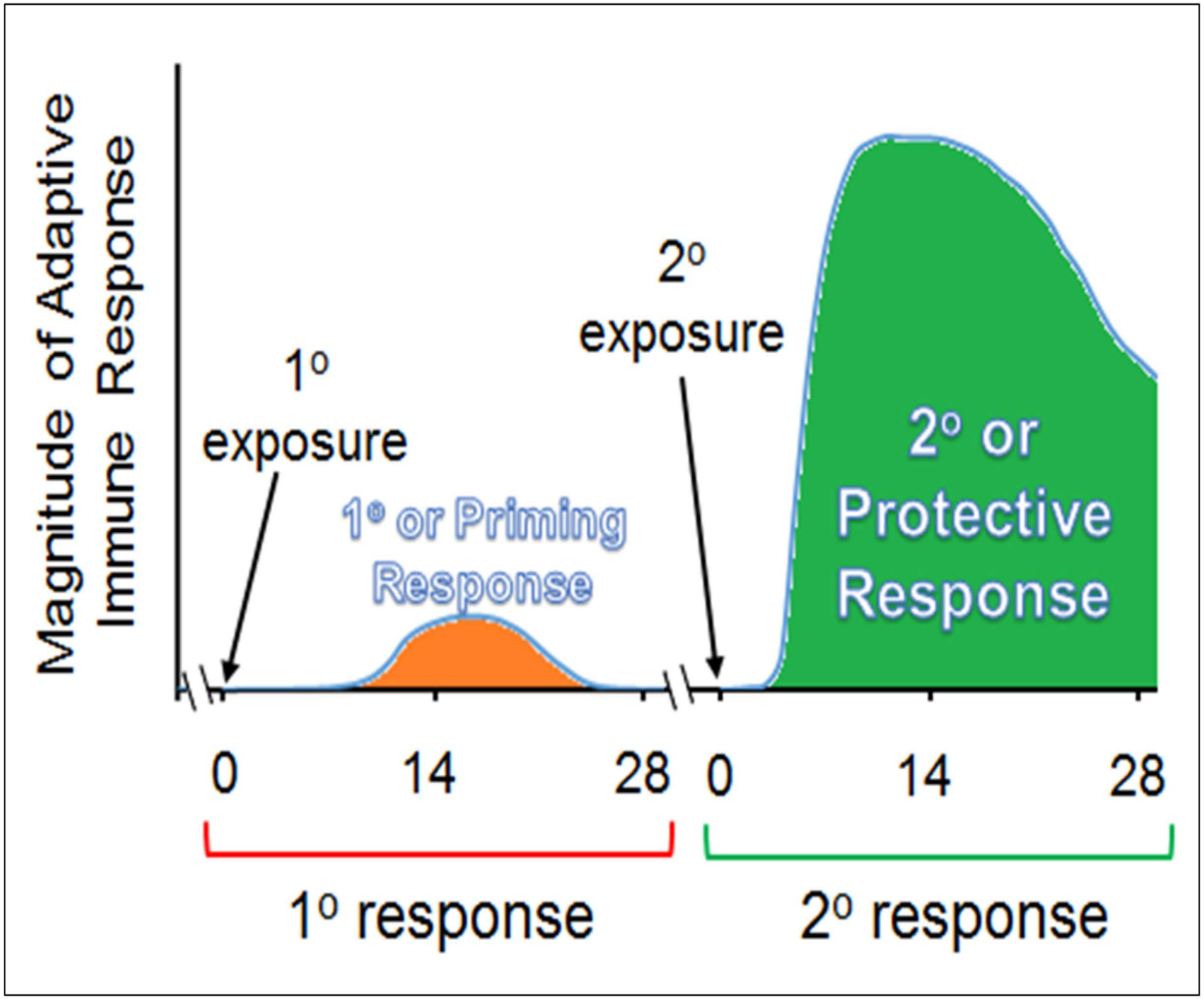

Figure 1: Secondary exposure of primed host usually results in robust adaptive immune system response that helps clear the pathogen. Usually secondary (2°) adaptive immune response peaks in 1-4 days but may be extended in some cases upto 10-14 days. Incidentally the peaking of 2° response in primed host appears to follow similar response time as that of incubation period of common communicable deadly diseases/pathogens in non-primed hosts (see Table 1).

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Table 1. Incubation period of selected infectious diseases #

S.No.	Disease	Onset of Disease in Days	Pathogen
1.	BUBONIC PLAGUE 'Black Death'	2 - 6 (1-3 in case of inhalation)	*Yersinia pestis*
2.	Yellow Fever	3–6	*Yellow fever virus* (YFV)
3.	Anthrax	1–7	*Bacillus anthracis*
4.	Small pox[1]	7-17 (usually 10 - 14)	*Vaccinia virus*
5.	Pneumonia[2]	1-3 (max 7-10)	*Streptococcus pneumoniae, Haemophilus influenzae* type b (Hib)
6.	Bacterial Meningitis and Sepsis	2 -10 (usually 3 – 7)	*Streptococcus pneumoniae, group B Streptococcus, Neisseria meningitidis, Haemophilus influenzae* type b (Hib) , *Listeria monocytogenes*
7a	Gastroenteritis/Diarrhea – *Early onset*	0.25-3	Viruses: *Noroviruses, Rotaviruses, Sapoviruses* Bacteria: *Bacillus cereus, Vibrio cholerae (O1; cholera), V. cholerae (non-O1), Clostridium perfringens, V. vulnificus, Clostridium botulinum, Escherichia coli (enteroinvasive infection - EIEC), E. coli* (enterotoxigenic, toxicoinfection-ETEC), *E. coli* (enteropathogenic infection) (EPEC)
7b	Gastroenteritis/Diarrhea – *Medium onset*	0.5 - 11	*Shigella sp., Campylobacter sp. Yersinia enterocolitica*
7c	Gastroenteritis/Diarrhea – *Late onset*	>3 – 14	Viruses: *Astroviruses* *Escherichia coli* O157:H7, *Cryptosporidium parvum*
8.	Respiratory viral infection	2-7	Various viruses
9.	Influenza	1-4	*Influenza virus*
10.	Gonorrhoea	2-7	*Neisseria gonorrhoeae*
11.	Rubella	8-10	*Rubella virus*
12.	Scarlet fever	1-3	group A *Streptococcus* or "group A strep."
13.	Malaria	7- vary	Various *Plasmodium sp.* Species causing severe forms show symptoms early.
14.	Mumps	12-26 (usually 18)	*Mumps virus*
15.	Rabies	3-8 weeks	Members of the family *Lyssavirus*
16.	Varicella (chickenpox)	10-21	*Varicella-zoster virus* (VZV)
17.	Measles	10-12	*Measles virus*

#from Centers for Disease Control and Prevention. USA. Web address: https://www.cdc.gov

1. Small pox does not occur anymore
2. 'Pneumonia is the top killer disease for children under the age of five years' [Revised WHO classification and treatment of childhood pneumonia at health facilities: QUICK REFERENCE GUIDE [Internet]. http://www.who.int/maternal_child_adolescent. 2016 [cited 13 August 2016]. Available from: http://worldpneumoniaday.org/wp-content/uploads/2014/10/WHO_Quick-reference-guide_Pneumonia_Sept-2014.pdf]