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Commentary

# The concept of commensal viruses almost 20 years later: redefining borders in clinical virology

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In 1999, P. Griffiths broached the concept of commensal viruses [1], concluding in the speculative editorial that 'we should not exclude the possibility that commensal viruses may exist'. Where are we, almost 20 years later?

The frontiers of clinical virology have been reshaped by the expansive potential of next-generation sequencing: characterizing viral genomes in samples spanning environmental, animal and human sciences [2]. So far, next-generation sequencing has identified novel viral aetiologies for distinct diseases such as Merkel cell polyomavirus [3], as well as implicating divergent viral strains in syndromes of previously unrecognized origin, such as astrovirus in central nervous system infection [4]. The technology has also contributed to the characterization of emerging viruses such as the Middle East respiratory syndrome coronavirus [5] and Ebola virus [6]. However, while next-generation sequencing is clarifying the viral aetiologies of some pathologies, the multitudes of unexpected viruses found in healthy subjects are blurring the definitions of Koch's postulates. Indeed, an unexpectedly abundant and diverse array of viral sequences has been found in asymptomatic control subjects, and immunocompromised patients without signs of overt disease [7,8]. Whereas the presence of viral partial genome sequences should be interpreted with caution, the identification of full-length genomes could partially replace the need for propagation of a pathogen in pure culture [9]. Over the past 20 years, mounting evidence of this diverse and abundant population of seemingly innocuous viral residents has confirmed the existence of commensal viruses, which together comprise the human virome.

Taking the examples cited by Griffiths [1], Torque tenovirus, a so-called orphan virus, is now considered as a surrogate marker of immune suppression in solid organ transplant recipients, although the exact mechanism by which immunity modulates Torque tenovirus replication is still unknown [10]. Pegivirus, formerly known as hepatitis G virus or GB virus C, is found at high titres in 1%–5% of healthy blood donors, and in up to 20% of donors in developing countries or in patients co-infected with human immunodeficiency virus (HIV) or hepatitis C virus. As a member of the *Flaviviridae* family, Pegivirus was initially thought to cause hepatitis but this has since been rejected. However, the absence of well-defined organ pathology does not equate to an absence of effect. Koch's monocausal dogma of infectious disease could not anticipate the complex effects that a virus may have on the host immune response. Pegivirus reduces the immune activation of T cells, B cells, natural killer cells and monocytes, ultimately leading to reduced progression of HIV infection and HIV-associated mortality [11]. Pegivirus is therefore a perfect example of a commensal virus, or how *the human virome could be more than a source of pathogens*, as reviewed by H.W Virgin [12]. Various reports have shown that the virome persists in a dynamic and subtle equilibrium with the immune system and other components of the microbiome, where cumulating permutations of stochastic infections and immune responses may build a distinct 'virotype' and 'immunophenotype' that are unique to each individual. By directly infecting cells of haematopoietic origin, Pegivirus interacts with the human immune system and, so, can hardly be considered as a silent bystander. Although some might argue that Pegivirus is 'innocent until proven guilty', the circumstantial evidence in the context of sound theoretical causality begs further investigation into its role in shaping our immunophenotype and virotype.

It is already well described how chronic stimulation by innate antigens may induce tolerance, notably through pathogen-associated molecular patterns. However, it is important to note that commensal gut flora do not only exhaust local immune cells into anergy but also actively induce a specific inflammatory suppression through T regulatory cells. Importantly, this immunomodulation is not only limited to the local environment but has lasting systemic effects that have been shown to influence

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immunocompetence in distant organs [13] and even alter host susceptibility to immune disorders such as asthma and type I diabetes [14]. This immunomodulation may also be used by co-infections to build symbiotic relationships. For example, chronic infection with gamma herpesvirus promotes resistance to *Listeria monocytogenes* and *Yersinia pestis* infection in mice [15]. On the other hand, co-infections may also team up against the host, such as is the case for cytomegalovirus and its potential to promote *Pneumocystis jiroveci* infection. Further, some *Leishmania* parasites have evolved to incorporate their immunomodulatory viral co-infection as an endosymbiont found within their cytoplasm: using the anti-viral inflammatory response as a virulence strategy to evade immune clearance [16]. These examples force us to rethink the effect that other viral endosymbionts (such as bacteriophages) have on the bacterial component of the microbiome.

Although the immune system can be an intermediary for pathogen cooperation, there also exists a rich network of direct interactions occurring between different inter-dependent microbial kingdoms, termed *transkingdom interactions.* Influenza virus enhances the superinfection of *Streptococcus pneumoniae* or *Staphylococcus aureus*, by exposing bacterial receptors on the cell surface through neuraminidase activity [17]. Similarly, murine norovirus directly interacts with bacterial antigens for B-cell attachment and infection [18]. Further, murine norovirus has been associated with inflammatory bowel disease in the presence of a host *Atg16L1* gene mutation, certain bacteria and environmental toxins [19]. This concept, called the 'virus-plus-susceptibility-gene' effect, adds another layer of complexity to the interactions of the human virome, where, in some circumstances, viral infections act in concert with host gene polymorphisms, the microbiome and environmental factors to modulate phenotypic variability. A particularly interesting mechanism of the interaction between viruses and host genetics has been found at the microRNA level. Several viruses produce 'mimic' microRNAs with sequences sufficiently compatible to mRNA targets that they may bind them to inhibit host transcription in a sequence-dependent manner [20]. Finally, besides its interactions with bacteria and its virus-plus-host-gene properties, murine norovirus also has the capacity to restore the physiological intestinal anatomy and lymphoid function in germ-free mice [21]. Murine norovirus may therefore harbour both detrimental and beneficial effects to the host through distinct mechanisms, and represents an exemplary model of the different influences of commensal viruses.

In recent years, the bacterial part of the human gut microbiome has been extensively studied. The gut virome component comprises predominantly bacteriophages but also contains diverse eukaryotic DNA and RNA viruses, including adenovirus, astrovirus, rotavirus, bocavirus, picornavirus, anellovirus and picobirnavirus [8]. Its content is highly influenced by environmental and dietary habits, with specific variations occurring during the first 2 years of life. Interestingly, although interpersonal diversity increases with age, intrapersonal variability seems to diminish [22–25]. In a recent review, Pfeiffer *et al.* depict how transkingdom interactions govern enteric viral infections, either by promoting viral replication and transmission or inducing viral clearance [26]. For instance, poliovirus replication is enhanced by direct contact with bacterial membrane components (lipopolysaccharide and peptidoglycans), which promote virion stabilization and cell attachment. Strikingly, there are data suggesting that a specific adaptive immune response is not necessarily required to clear viral infection: rotavirus can be cleared by bacterial flagellin through Toll-like receptor signalling and induction of interleukins 18 and 22 or by synergy between interleukin-22 and interferon-λ. Considering the pathology-changing influence of microbial alterations on viral infection, transkingdom interactions should be further explored for their potential as clinical tools, which we could term *interbiotics*.

The human respiratory virome is also the site of complex interactions between bacteria and community-acquired respiratory viruses [17]. Interestingly, community-acquired respiratory viruses have been identified in children with unexplained fever, as well as in afebrile controls, again raising the question of the spectrum of associated diseases and the way viruses may express their pathogenic role [27]. In clinical practice, determining the prevalence of asymptomatic community-acquired respiratory virus infection and the whys and wherefores of their pathogenic role is of utmost importance especially given the prevalence of these infections.

In conclusion, we have made serious advances in identifying the viral components of the human virome, which has given us a preview of their role and influence on the host and its microbiome: not only altering the virulence of co-infecting pathogens, but also potentially affecting host gene transcription and undoubtedly contributing to the nuance of our immunophenotype. Hence, the human virome is clearly more than a collection of pathogens. Research in the field should take into account viruses together with, and not apart from, their surrounding environment, and particularly in the case of apparently 'inoffensive' infection. Although there is certainly a dynamic overlap between its commensal and pathogenic members, the virome has been revealed as an intricate network of pathology-changing interactions that could soon prove to be of clinical significance.

## Author contributions

DLV elaborated and wrote the manuscript, LK provided edits, revisions and mentorship.

## Transparency declaration

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