Virus–host interactions and their roles in coral reef health and disease

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Abstract | Coral reefs occur in nutrient-poor shallow waters, constitute biodiversity and productivity hotspots, and are threatened by anthropogenic disturbance. This Review provides an introduction to coral reef virology and emphasizes the links between viruses, coral mortality and reef ecosystem decline. We describe the distinctive benthic-associated and water-column-associated viromes that are unique to coral reefs, which have received less attention than viruses in open-ocean systems. We hypothesize that viruses of bacteria and eukaryotes dynamically interact with their hosts in the water column and with scleractinian (stony) corals to influence microbial community dynamics, coral bleaching and disease, and reef biogeochemical cycling. Last, we outline how marine viruses are an integral part of the reef system and suggest that the influence of viruses on reef function is an essential component of these globally important environments.

Top-down effects
The ecological concept that organismal growth and abundance are primarily regulated by predation (for example, grazing and viral infection) as opposed to resource limitation.

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Viruses infect all cellular life, including bacteria and eukaryotes, and contain ~200 megatonnes of carbon globally[1] — thus, they are integral parts of marine ecosystems[2,3]. Since the discovery of the remarkably high abundance and widespread occurrence of viruses in sea water in the 1980s[4], ocean viruses have been intensively studied, with research focusing on the effects of viruses on biogeochemical processes and ecosystem function, and their top-down effects on microbial food webs (BOX 1).

Most marine virology has focused on pelagic open-ocean systems and temperate coastal seas, but the virology of coral reefs has started to gain attention only during the past 15 years. Tropical shallow reef environments are coastal benthic habitats that, although constituting less than 0.5% of the ocean seabed, contain approximately 25% of all marine species. These diverse habitats are dominated by scleractinian (stony) corals and other sessile invertebrate organisms such as soft corals and sponges, in addition to macroalgae. Importantly, stony corals build the foundation of the reef and release large amounts of carbon, and perhaps nitrogen, to the surrounding environment[5]. In the open ocean, bacterioplankton and therefore phages dominate research efforts, whereas on coral reefs virologists often examine eukaryotic viruses and phages that are associated with benthic stony corals and their inhabitants, as well as the viruses that are associated with the water column that bathes these macroorganisms. Little is known about viral interaction or exchange between the benthic zone and the water column in reef systems. However, there is evidence that macroorganisms play important parts in the dynamics of viroplankton; for example, sponges can filter and consume viruses[6,7].

This Review summarizes our current knowledge of viruses in tropical coral reef ecosystems. Drawing on marine virology and coral reef biology research, we discuss when and how viral consortia shift on reefs and how this may affect the health and function of coral reef ecosystems. We discuss the dynamics of coral reef virology through the lens of coral reef decline, which has been a cause for increasing concern worldwide since the late 1970s and is primarily driven by climate change, overfishing and nutrient pollution[8–10]. To conclude, we highlight the interconnection between viral infection in reef hosts and concentrations of nutrients and community diversity in reef sea water.

The coral reef ecosystem

Tropical coral reefs occur in nutrient-poor environments, but they still form highly productive and diverse ecosystems[11,12]. This observation of an ecosystem with high biodiversity and low nutrient input is known as Darwin's paradox[13]. In healthy reefs, marine microbial communities are the 'solution' to this apparent paradox: marine phytoplankton in the water column[14] together with dinoflagellate endosymbiotic algae in the genus *Symbiodinium*, which leak up to 95% of their photosynthesized sugars into coral tissues[15], provide their habitats and hosts with the energy that is required to construct substantial reef frameworks. Corals also harbour a diversity of symbiotic bacteria and viruses in their

Box 1 | **Marine virology**

The ocean is estimated to contain an average of 10^7 viruses ml^{-1}, which is approximately an order of magnitude more than the number of microbial cells per millilitre, depending on the habitat[119–122]. Viruses can infect all cellular life forms, from animals and plants to microorganisms, including protists, bacteria and archaea. Increasing evidence suggests that viruses are important agents of mortality for marine microorganisms[120,123–125]. Approximately 10^{23} microorganisms are infected every second in the oceans[126]. Each viral infection leads to the production of new viruses, and empirical studies have calculated that viral production rates average at 10^{11} viruses l^{-1} d^{-1} in marine ecosystems[63,72,73,75,121,127,128].

Sustained viral production in marine systems exerts strong pressures on oceanic life across all trophic levels[83]. Viral infection can remove up to 26% of photosynthetically fixed carbon by phytoplankton and 20–50% of bacterial standing stock daily in the oceans[120,121,124,129]. Through infection and the lysis of microorganisms, viruses release dissolved organic matter and nutrients[130–133], making them available for other microorganisms. This control decreases energy transfer to higher trophic levels and increases microbial activity and growth[71]. This 'viral shunt' is particularly important when resources are limited, such as in oligotrophic sea water[1,126]. Viruses are also important because they can control the population structure and diversity of their hosts through 'kill-the-winner' mechanisms[79]. In this model, viruses remove the most competitive and dominant taxa through infection, which allows the growth of less-competitive microorganisms and maintains diversity[80,82]. A classic example of this process is the termination of monoclonal phytoplankton blooms by viruses[134–136].

Many viruses can also interact with their hosts through lysogeny, by integrating their genomes into their host genome. Lysogenic infection is prevalent in the oceans, although the quantitative importance of this process varies across time and space. Very little is known about the factors that trigger lysogenic versus lytic infections in nature. However, it has been suggested that lysogeny enables viruses to survive when host growth and abundance are low. This lysogenization of microorganisms can be beneficial for hosts: it can protect them from other viruses and/or boost their metabolism and survival through the expression of auxiliary metabolic genes that are encoded in viral genomes. Lysogenic conversion increases microbial abundance and growth in coral reefs in a process called 'piggyback the winner' (REF. 70).

Marine viruses are morphologically and genetically diverse. In their simplest form, viruses consist of a protein capsid that encapsulates their genetic material, which is either DNA or RNA. In marine samples, transmission electron microscopy (TEM)-based studies have shown that viral capsids have a broad range of sizes, shapes and features[64,120]. Most marine virus-like particles (VLPs) range between 26 nm and 129 nm in size[137], with non-tailed viruses representing 50–90% of morphotypes[138]. Molecular tools have rapidly outpaced morphological studies to reveal the previously unknown, vast genetic diversity of marine phage and eukaryotic viruses[1,65,68,120,126,137,139–149]. Targeted studies amplified structural and functional viral genes to reveal the vast diversity of DNA and RNA viruses that infect protists and bacteria[1,65,126,146,150–152]. In addition, metagenomic surveys show that viruses are a vast reservoir of genetic diversity in the oceans[65,126,137,139–141,144,145,148,149]. For example, metagenomic analysis of 184 double-stranded DNA viral assemblages revealed the extraordinarily high level of phage genetic diversity (up to 12.9×10^4 distinct genotypes)[139], and a survey of single-stranded DNA viruses uncovered more than 129 genetically novel and distinct virus types that are major pathogens of marine animals and plants[149]. Most recently, viral protein sequence clusters that were retrieved from natural marine assemblages revealed that the global ocean is likely to harbour up to 5,476 dominant lineages[137].

Benthic
Related to the seafloor habitat, including the objects and organisms that are associated within or on it.

Eukaryotic viruses
Viruses that infect eukaryotic organisms.

Microbial communities
Assemblages of populations of interacting microscopic species, potentially including representatives from all three domains (bacteria, archaea and microscopic eukaryotes) that occupy the same space at a particular time.

Symbiodinium
A genus of photosynthetic dinoflagellate algae that lives inside the tissues of corals and other marine hosts and provides them with fixed carbon. When lost en masse from a host, that host individual experiences diminished health and appears white or 'bleached'.

Coral holobiont
A host organism and all of the symbiotic microbial communities and viral consortia that live in and on it.

Coral surface microlayer
(CSM). A thin layer (several millimetres thick) at the interface between a coral colony and the external environment, which is rich in mucus and heavily colonized by bacteria and bacteriophages.

tissues and on their mucus-coated surfaces. Much of the past 20 years of coral reef microbiology has focused on bacterial members of the coral holobiont. These proposed mutualists and commensal symbionts contribute novel metabolic functions to their hosts, including nitrogen fixation, photosynthesis and the exclusion of potential pathogens from the coral surface microlayer (CSM)[16]. Healthy corals create the CSM by releasing large amounts of mucus consisting of glycoproteins[17], which coat colony surfaces in a manner similar to the mucosal layer in the human gut. In addition to harbouring microbial symbionts and providing them with a source of nutrients, the CSM is an important physical barrier that protects coral colonies from desiccation, abrasion and fouling[18].

Acute environmental stress can trigger corals to release large volumes of mucus[5,19–23], which is energetically costly. Abiotic stressors can also disrupt the mutualistic interactions between the coral hosts and their microbiota and lead to substantial decreases in symbiont abundance and/or shifts in their community composition[24–26]. Coral 'bleaching' specifically describes the gross loss of the algal *Symbiodinium* cells and/or chlorophyll from a host; this process ultimately gives the host a pale or whitened appearance[27]. If a bleached host does not recover its symbiotic community in weeks to months after bleaching, disease and partial or total host mortality results.

In 2014–2016, during the global coral bleaching event, mass mortality was observed in reefs worldwide, due to continuously increased sea-surface temperatures that arose from global climate change and the concomitant strong El Niño event. Anomalous temperatures, algal competition or exposure to increased levels of inorganic nutrients, such as nitrate and phosphate, can also lead to the dominance of opportunistic or pathogenic bacterial communities, the loss of beneficial symbiont-derived metabolic functions and/or coral disease and mortality[28–31].

Distinct microbial communities are found in specific locations in reef ecosystems (for example, the benthos versus the adjacent water column). The reef benthos and water column compartments each teem with a tremendous number and diversity of viruses, bacteria, archaea and protists. Heterotrophic bacteria, archaea and viruses transfer the primary productivity that is generated in the benthic compartment by *Symbiodinium* spp. and cyanobacteria across reef ecosystems by stimulating

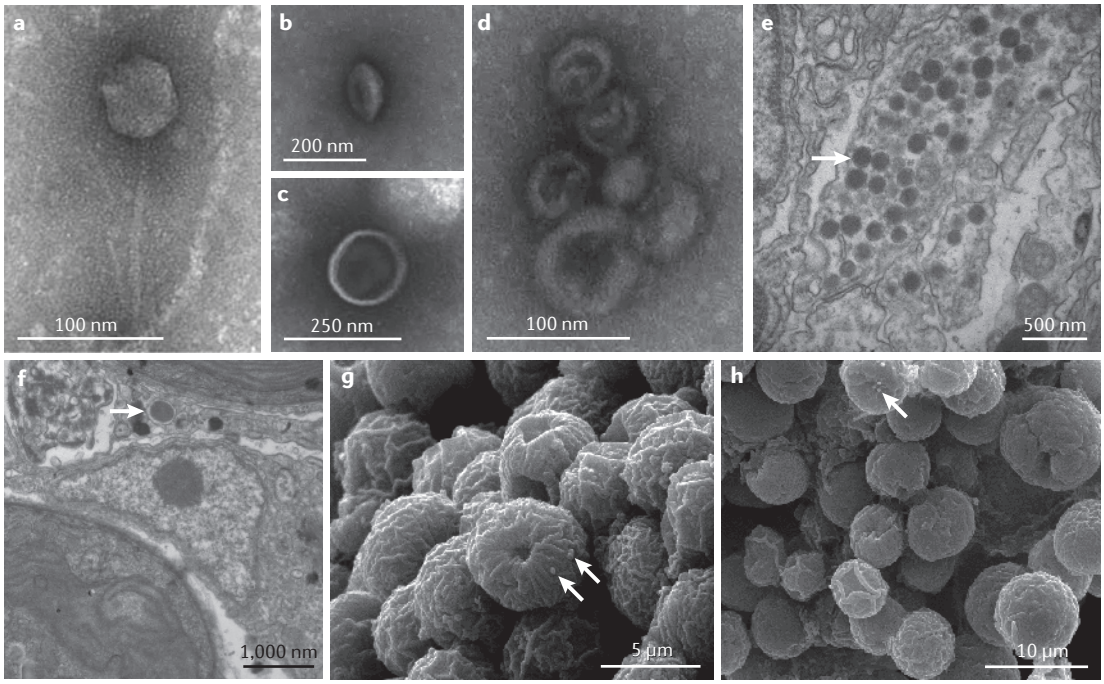

Figure 1 | **Transmission electron microscopy images of several types of coral-associated viruses.** Virus-like particles, including a myophage (part **a**), an archaeal virus (part **b**), an Irido-like virus (part **c**) and retro-like viruses (part **d**), were found in the coral surface microlayer (CSM) of diseased *Porites lobata* corals. Arrows indicate atypical herpes-like virus particles (part **e**) and a mega-like virus in stressed *Acropora* spp. coral tissues (part **f**). Scanning electron microscopy has also revealed virus-like particles (indicated by arrows) that are associated with control (part **g**) and ultraviolet-C irradiated (part **h**) *Symbiodinium* spp. cultures. Transmission electron microscopy images in parts **a**–**d**, courtesy of C. Couch, University of Hawaii, USA. Part **e** adapted from REF. 46.

energy fluxes, the cycling of essential elements (carbon, nitrogen, phosphorus and sulfur) and the release of important metabolites to the water column through the microbial loop and viral shunt[19,21,32–34]. Although years of research have identified these and other important roles and interactions among primary producers and heterotrophic bacteria in coral reef benthos, the roles of viruses in reefs are just beginning to be appreciated.

The coral reef virome

The benthic compartment: scleractinian coral virology and ecology. Coral holobionts contain many different virus-like particles (VLPs; FIG. 1). However, VLPs were first observed in the cnidarian relatives of stony corals, the sea anemones[35]. Transmission electron microscopy (TEM) found that cnidarian tissues contained viruses that were predominately ~60 nm in diameter, icosahedral and electron dense. These viruses were hypothesized to infect the host tissues, as sea anemones do not harbour endosymbionts, unlike their stony coral relatives. Later, VLPs were morphologically characterized from control and thermally stressed coral animals; control coral VLPs were predominantly 30–40 nm and 50–60 nm in diameter, whereas stressed animals had larger (40–50 nm and 60–80 nm) and more abundant VLPs[36]. These larger viruses were proposed to infect the dinoflagellate endosymbionts of corals, which suggests a link between temperature stress, viral infection and bleaching.

Since these two landmark findings, other microscopy-based and 'omics'-based studies have identified a broad diversity of viruses on, and in, corals (FIG. 2). Microscopy work has revealed that viruses infect coral tissues and the CSM[37–41]. The viruses in the CSM seem to be more diverse than those that are associated with coral tissues, perhaps owing to enrichment with viruses from the water column[42]. In a quantitative and comparative study, 17 subgroups of viruses from two genera were associated with the CSM of coral colonies. Many recovered VLPs were similar to phages and archaeal viruses, which provided one of the first indications that CSM-associated phages may protect the coral host from microbial pathogens[43] (see below). TEM and other approaches (for example, flow cytometry) have also identified VLPs that are associated with cultures of *Symbiodinium* cells isolated from corals and other cnidarians[41,44,45].

However, TEM images (FIG. 1) only provide informed guesses about the true evolutionary relationships of coral-associated viruses. This is because virus taxonomy based exclusively on TEM can incorrectly link groups of viruses with conserved phenotypes but widely different phylogenies. Because capsid size and shape can vary and overlap within and between viral families, TEM-based studies may not fully resolve a group of VLPs to biologically meaningful taxonomic groups (that is, to the family or genus levels)[46].

Since the mid-2000s, metagenomics, transcriptomics and proteomics have begun to assess which groups of

Viral shunt
A process in which viruses release dissolved organic matter and inorganic nutrients through the infection and lysis of microorganisms, making them available to other nearby microorganisms. This reduces energy transfer to higher trophic levels and increases microbial activity and growth through the recycling of key elements.

Cnidarian
Related to a basal animal phylum that contains the stony corals and other closely related taxa that are united by the possession of stinging cells. Examples include soft corals, anemones, hydra and jellies.

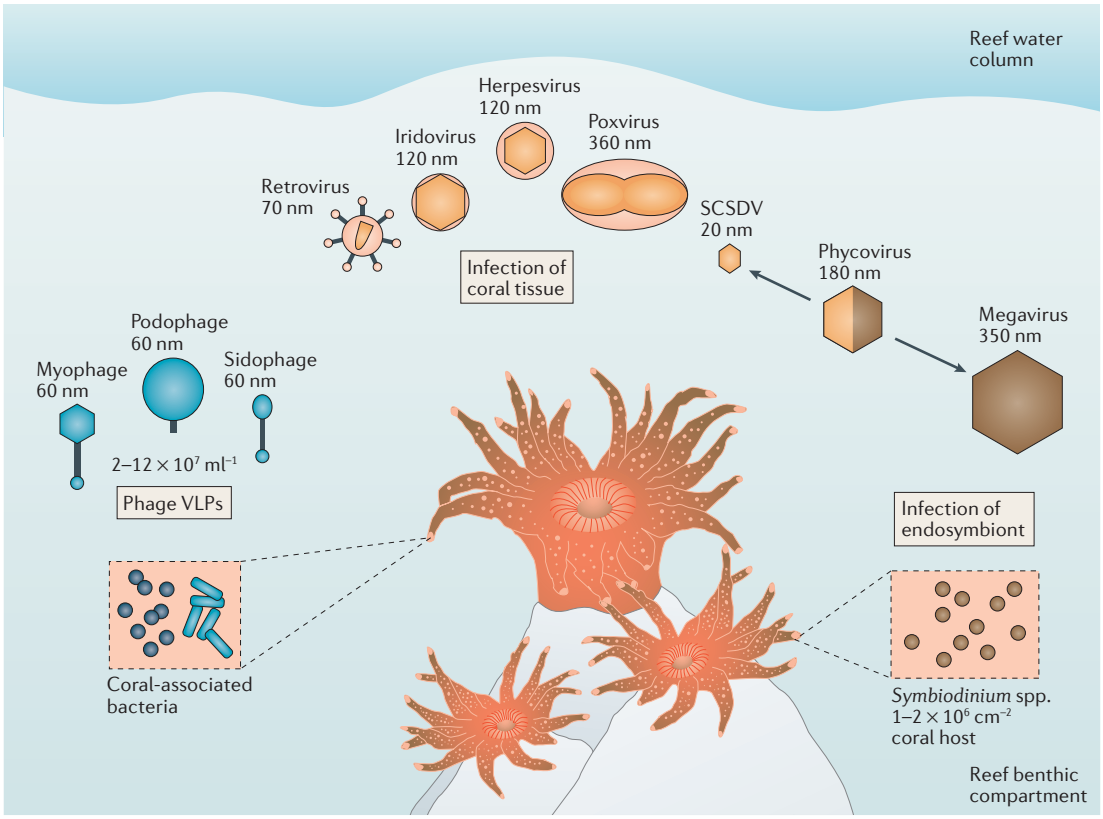

Figure 2 | **The core coral virome in the benthic compartment of shallow-water tropical coral reefs.** The viruses depicted are representative of those that are commonly found, but this is not a comprehensive listing of all groups that occur in this environment. The host colours correspond to the main virus groups that are hypothesized to infect them: blue represents viruses that infect coral-associated bacteria, orange represents those that infect the coral host and brown represents those that infect algal endosymbionts of corals. Approximate virus particle sizes (in nanometres) and abundances for each of these groups of viruses are also provided. Data from REFS 38,46,63,111,153,154,161. SCSDV, small circular single-stranded DNA virus; VLPs, virus-like particles.

viruses are present in corals and how they differ across host taxa, locations, host health states and after environmental disturbance[46–61]. Although the sampling and analysis of coral viromes has been reasonably comprehensive (with perhaps the exception of RNA virus analysis), comparing omics-based studies is challenging. Much of this challenge stems from a lack of standardization among omics methods, which is driven by continual efforts to improve the application of these techniques. Different omics techniques may vary in their requirements for specific steps that enrich for, or eliminate, some viral genomic sequences. Research groups may use (or sometimes entirely skip) different preservation, particle purification and/or amplification methods (for example, ϕ29 DNA polymerase). Studies also differ in the sequencing platforms, bioinformatic pipelines and quality-control measures that are used, which limits our ability to compare coral reef virus studies[49].

Nevertheless, a picture of the standard or 'core' coral virome has emerged (FIG. 2). A recent meta-analysis[49] found that ~60 virus families (~58% of all families) are present in corals around the world, out of the 7 orders, 104 families and 410 genera of viruses that are currently recognized by the International Committee on the Taxonomy of Viruses (ICTV)[62]. Based on a stringent threshold (≥90% prevalence among studies), the core coral virome comprises only 9–12 families in three major viral lineages: double-stranded DNA (dsDNA) group I, single-stranded DNA (ssDNA) group II and retrovirus group IV[46]. Metagenomic and transcriptomic data[49] indicate that all coral samples contain dsDNA tailed phages of the *Caudovirales* order, in particular the dominant *Siphoviridae*, *Podoviridae* and *Myoviridae* families. Out of all of the viruses that infect eukaryotes, nucleocytoplasmic large DNA viruses (NCLDVs; proposed order *Megavirales*) are ubiquitous. The *Phycodnaviridae* and *Mimiviridae* NCLDV families were present in all samples, and the *Poxviridae*, *Iridoviridae* and *Ascoviridae* NCLDV families were detected in 90% of samples. Atypical viruses related to the *Herpesvirales* order (which is composed of the *Alloherpesviridae*, *Herpesviridae* and *Malacoherpesviridae* families) are also members of the core coral virome; sequences that are similar to this virus group were found in 98% of the libraries[46]. These herpes-like viruses are considered to be atypical because they are morphologically indistinguishable from herpesviruses in TEM images but

Viromes
The ensembles of viruses in specific samples.

Nucleocytoplasmic large DNA viruses
(NCLDVs). A monophyletic group of ten virus families that have a common virion and genomic structure and replicate in the nucleus of their hosts, but their particles form in the host cytoplasm.

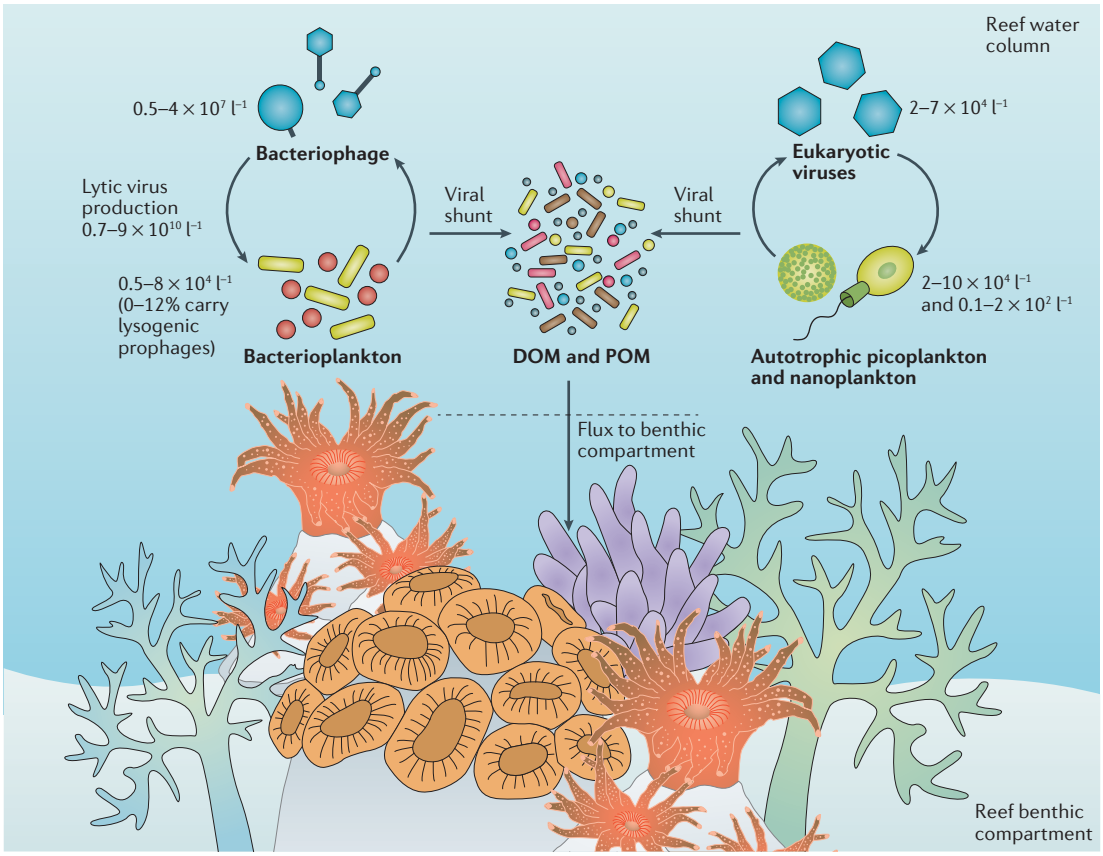

Figure 3 | **Viruses in the water column of tropical reefs.** The figure summarizes the abundances of key virus groups (bacteriophages and eukaryotic viruses) that are associated with the water column compartment of shallow-water tropical reefs. Host abundance and estimates of viral production (phage only) are also provided. Through the infection and lysis of microorganisms, these viruses release dissolved organic matter (DOM) and nutrients[130–133], making them available for other microorganisms in the reef water column and benthic compartments. This control decreases energy transfer to higher trophic levels and increases microbial activity and growth through the recycling of key elements[71]. This viral shunt is particularly important when resources are limited, such as in oligotrophic sea water[1,126]. Data from REFS 63,70,76. POM, particulate organic matter.

have never been observed in coral cell nuclei, where herpesviruses typically replicate[46]. Furthermore, most herpesvirus-related sequences from coral viromes only resemble a narrow section of reference genomes (mainly Suid herpesvirus 1)[49].

Genomic signatures from some ssDNA (for example, *Circoviridae*) and ssRNA (for example, *Retroviridae* and *Caulimoviridae*) viral lineages are also well represented, but are not found in 90% of the corals sampled to date; this may be due to methodological differences among studies[46,48,49]. For example, annotations to small circular ssDNA viruses (SCSDVs) are not found in the transcriptomes of corals but were found in viral purified DNA libraries. The use of mRNA polyadenylation or transcript size selection is likely to prevent the detection of SCSDVs from transcriptomes. Putative retroviruses are also often removed from annotations because of the difficulty in determining whether they represent true viral sequences or retro-elements that are associated with coral host genomes. Recent research suggests that at least some of the retroviral sequences are indeed true retroviruses[46,53,58]. Given these issues, it may be necessary to re-analyse existing coral virome data sets in ways that ensure the potential signatures of ssDNA and ssRNA viruses are not discarded and/or to apply a different criterion to determine whether these virus types merit inclusion in the core coral virome.

The water column compartment: reef seawater viral ecology. Virus abundance, structure and rates of lytic infection vary across reef habitats[63]. In reef sea water, it has been estimated that there are about 10^6–10^8 viruses ml^{-1}, outnumbering other microbial counterparts by an order of magnitude or more (FIG. 3). Many reef seawater viruses are morphologically and genetically similar to those on and within corals, whereas others are distinct. For example, a TEM-based study identified up to 26 distinct VLP morphotypes of various sizes in reef sea water from Kāneʻohe Bay in Hawaii in the United States, as well as in the corals that reside there[60]. These included tailed and non-tailed icosahedral VLPs, as well as filamentous, rod-shaped and lemon-shaped VLPs. Most reef seawater VLPs were putative phages in the *Podoviridae*, *Myoviridae* and *Siphoviridae* families[62,64]. Putative eukaryotic viruses in

Phycodnavirus
One of a family of nucleocytoplasmic large DNA viruses that commonly infects marine phytoplankton and coral holobionts. Phycodnaviruses are also known as phycoviruses.

Megaviruses
A proposed order of monophyletic viruses that is relatively large in terms of physical size and genome length.

Bacterial standing stock
The number of bacterial cells in a region at any one time.

Bacterial turnover
The time it takes for bacterial standing stock to be replaced through production and predation.

Temperate viruses
Viruses that integrate their genome into the chromosome of their host as a prophage and replicate silently along with their host.

the *Phycodnaviridae* and *Herpesviridae* families were observed; these families are also in the core coral virome. However, the eukaryotic virus family *Geminiviridae* — as well as the families *Fuselloviridae* and *Salterproviridae*, which are thought to infect archaea — were common in the reef water column, but not in corals.

Molecular investigations into the diversity of viruses in tropical reef waters have relied primarily on marker-gene surveys and metagenomics. Surveys that targeted the viral RNA-dependent RNA polymerase gene, as well as shotgun sequencing, revealed novel ssRNA viruses in tropical oceans, with the vast majority of them belonging to the *Picornaviridae*, a family of ssRNA viruses that infect marine protists[65,66]. A survey that targeted the DNA polymerase gene of members of the *Phycodnaviridae* also revealed the presence of diverse and largely novel populations of dsDNA viruses that infect eukaryotic phytoplankton in coastal Hawaiian waters[67]. Whether these viruses also infect corals is currently unknown, but the detection of diverse picornavirus-like and phycodnavirus-like sequences in these tropical waters is consistent with the importance of dinoflagellates, diatoms and other protists in these systems, and it indicates that viruses can have a strong influence on primary production in coral reefs.

In addition, metagenomic surveys of dsDNA viral assemblages have enabled unprecedented views of the taxonomic and functional diversity of viruses in coral reef sea water. dsDNA viral sequences that have been detected in reef waters include the bacteria-infecting *Microviridae*, *Myoviridae*, *Podoviridae* and *Siphoviridae* families[49,57], as well as phytoplankton-infecting NCLDVs, which are dominated by megaviruses, *Phycodnaviridae* (Prasinovirus spp. in particular), *Iridoviridae* and *Mimiviridae*[46,49,53,56,68]. Other studies have also found diverse eukaryote-infecting ssDNA viruses from the family *Circoviridae*[56]. Last, metagenomic analysis of dsDNA viruses has enabled the detection of potentially lysogenic viruses in tropical coastal waters[69,70]. Together, these studies provide snapshots of the morphological, functional and taxonomic diversity of viruses in waters that are associated with coral reef ecosystems. However, considerable work remains to assess the extent of virus diversity and function in reef waters, as well as their environmental determinants.

The virome and coral reef health

The water column compartment: viral infection and shallow-water reef ecosystem function. Viral infection and lysis of bacterial hosts removes substantial amounts of bacterial standing stock daily. On average, virus-mediated bacterial turnover rates on remote Polynesian island reefs are upwards of 20–120% of the daily standing stock, depending on location[63]. Lytic infection activity not only removes bacterial hosts but also releases organic matter and inorganic nutrients into the surrounding sea water, making them available to other, uninfected microorganisms. This top-down control decreases the transfer of energy to higher trophic levels and increases microbial activity and growth through the recycling of key elements[71]. Furthermore, viral lysis substantially contributes to the pool of reef water dissolved organic carbon (DOC), with estimates suggesting that 1–62 μg of DOC l^{-1} day^{-1} are released through lytic infection[63]. These estimates are at levels similar to those found in nutrient-rich temperate waters and are 1–90-fold higher than previous reports of organic carbon release in marine ecosystems as a result of viral lysis[72–77]. However, further work is needed to evaluate the amount of microbial mortality that is induced by viruses and quantitatively assess how viruses contribute to the release of DOC in coral reef ecosystems, as only one study has quantified these processes so far[63]. Importantly, these values represent ~10% of total gross benthic carbon fixation[78], which demonstrates the remarkable influence of viruses on reef biogeochemical cycling.

It should be noted that the above values are for lytic infections only; thus, they are likely to underestimate the contribution of temperate (lysogenic) viruses to bacterial turnover and carbon recycling on reefs. For example, between 2% and 89% of bacteria were reported to be lysogenized in a tropical reef atoll system[76]. A recent study[70] investigated both viral lytic and lysogenic infections across 24 reef viral assemblages and reported a high prevalence of temperate viruses in conditions that support high microbial densities. Statistical modelling of these reef viromes, including the frequency of lysogenic cells, as well as the proportion and diversity of lytic and lysogenic viral marker genes, revealed a clear switch from viral lytic to lysogenic infections with increased microbial densities[70]. This new finding challenged the classic view of the 'kill-the-winner'

Box 2 | Coral phages: guardians of the host or mediators of infection?

Corals produce copious amounts of mucus, a substance that is composed of sugars, mucin glycoproteins and other metabolites. Mucus protects and buffers colonies against the environment and also acts as a nutritional resource and chemical signal to microbial symbionts[5,19–21,23]. In the coral surface microlayer (CSM) there are approximately $2–5 \times 10^6$ bacteria ml^{-1} and $0.1–3 \times 10^7$ virus-like particles (VLPs) ml^{-1}; this is about 10–100-fold more bacteria and viruses than in the water column[38,39,153,154]. Phages are core members of the coral virome; however, unlike the eukaryotic viruses, which have been correlated with some aspects of disease and bleaching, the roles of coral-associated phages remain more enigmatic. Given what is known about the general roles of phages in marine microbial ecology, we predict that phages have a dual role in corals by infecting, lysing and modulating bacterial hosts[92], and, in the process, releasing nutrients.

Thus far, most studies have focused on phages as an important top-down control of potentially invasive and virulent bacteria. For example, one study[155] found that virus/bacteria cell ratios are ~4.5-fold higher in the CSM than in the overlying water column. It also found that phage adherence to bacteria, through C-type lectins and immunoglobulin-like domains, decreased rates of microbial colonization and pathogenesis on corals. Thus, phages exclude certain bacteria from the CSM by infecting and lysing these potential invaders[43]. However, it remains unknown how lysis of this microbial community contributes to shifts in carbon and nitrogen flux in the reef ecosystem.

Applied experiments using phages to mitigate disease have been attempted on a small scale[156–158]. The earliest studies used phages to control diseases caused by *Vibrio* spp. in corals from the Red Sea. This form of 'phage therapy' has been suggested to be useful for controlling outbreaks of disease-causing bacteria in natural settings[157,158]. However, the aetiological agents of most coral diseases remain unknown, and many are difficult to culture. Therefore, even identifying the phages and their target host bacteria *in situ* will be challenging. However, network or correlation analysis has provided us with a method to determine *in silico* potential interactions among

model[79,80], in which lytic viruses typically dominate viral assemblages in conditions with high microbial proliferation (BOX 2). This switch from lytic to lysogenic viral infection has been proposed as a mechanism to stimulate reef microbialization, in which temperate viruses protect their abundant host cells against infections from lytic viruses[70]. Increasing evidence indicates that this novel virus–host dynamic is widespread across ecosystems and is now known as the 'piggyback-the-winner' model[70]. Thus, it seems that temperate viruses are highly prevalent in reef ecosystems and, similar to their lytic counterparts, may have important roles in shaping reef microbial communities.

However, additional research is needed to fully assess viral life cycle dynamics in coral reef systems across space and time. We anticipate that the high viral infection activity in coral reef ecosystems is likely to shape the structure and diversity of the microbial host community, in a similar way to that described in other marine environments[81–83].

Another consequence of high rates of viral infection in reef ecosystems is the potential for viruses to mediate the transfer of genetic material between microorganisms. Besides affecting microbial population dynamics, marine viruses have a major role in microbial evolution through horizontal gene transfer or transduction[84,85]. In fact, studies have demonstrated that viruses may increase rates of horizontal gene transfer between microorganisms by as much as one million times in subtropical environments[86]. Virus-mediated horizontal gene transfer occurs at high rates in the oceans, with estimated rates of up to 10^{14} transduction events per year in the Tampa Bay estuary in Florida in the United States[86].

Viruses can also encode auxiliary metabolic genes that are involved in photosynthesis, carbon metabolism and nucleotide metabolism, which enhance microbial host growth and fitness[87–90]. The integration of viral genomes into the genome of a host through lysogenic conversion can thus manipulate host function. Also, it has been proposed that temperate viruses transcribe genes that suppress host metabolism to conserve resources under nutrient-poor conditions[91]. Thus, it is reasonable to hypothesize that viruses that act as genetic transfer agents may boost the metabolic abilities of their microbial hosts in nutrient-rich reef waters. One can also imagine that rapid genetic exchange and adaptation to changing conditions in tropical waters may increase the virulence of microbial communities. For example, phage-encoded toxin genes have been detected in the coral-associated bacterium *Vibrio coralliilyticus*, and virulence factors located on chromosomal pathogenicity islands also exist in some strains of this species[92].

The benthic compartment: implications of viral infection in corals on ecosystem function. Corals are predicted to influence biogeochemical processes in reef ecosystems because they release DOC and mucus exudates, which contribute to a pool of available nutrients in an otherwise oligotrophic reef habitat[19,93,94]. The influence of exudates from corals and other organisms on overall reef health and ecosystem-level metabolism is a current topic of intense study[95,96], particularly in regards to the role of DOC in stimulating the growth of bacterial lineages that are either beneficial or detrimental to reef health in the overlying water column and adjacent sediments[96–98]. This line of inquiry includes quantifying the amount of DOC that is released into the environment. The amount of DOC that is released from corals ranges between 8 and 56 μmol dm^{-2} d^{-1}, or ~10% of the total carbon fixed daily by corals[96]. Recent hypotheses suggest that macroalgae also secrete DOC, which increases the growth and oxygen consumption of bacteria, ultimately harming corals through the creation of hypoxic conditions on and near colonies[97,99–102]. Processes that increase DOC flux or the release of nutrients from the CSM thus have the potential to negatively feed back on coral reefs[97,101].

The role of corals in nitrogen cycling is less well understood. Although corals have been shown to be involved in many aspects of nitrogen cycling on reefs[47,103–106], they are largely regarded as nitrogen sinks[103]. However, mucus released from corals, much of which dissolves on release, contains large amounts of nitrogen (220 ± 40 mM (REFS 19,107)). One reason the role of corals as nitrogen sources is not well defined is that once nitrogen is released from corals, this nutrient is rapidly taken up by biota in the nitrogen-depleted oligotrophic environment; reef waters often only contain ~0.02 μM of ammonium, nitrate and nitrite[108]. The role of nitrogen flux in reef health is less clear than that of DOC flux. For example, one study[97] found that nitrogen has little to no role in coral mortality. However, nitrogen substantially affects reef health by increasing the prevalence and severity of disease and bleaching[109]. Importantly, excess nitrogen is effective at inducing the production of coral-associated eukaryotic viruses[110]. Thus, it is likely that changes in nutrient concentrations in reefs can increase levels of viral infection, with effects on coral health.

Viruses reduce coral reef health through bleaching and disease. Shifts in virus community composition and abundance are likely to correlate with differences in coral health and the reef at large. Substantial differences in the relative abundances of different groups of eukaryotic viruses and phages have been documented in lab-stressed corals from Hawaii and Florida[53] and also in bleached, diseased and healthy corals from Caribbean[56,57] and Pacific[111,112] reefs. If methodologically similar studies are compared, some virus families are ubiquitous in healthy, bleached and diseased corals (FIG. 4). Viral gene signatures indicate that an atypical relative of the *Herpesviridae* family is the most abundant virus family in healthy and bleached corals, and the second-most abundant in diseased corals (FIG. 4). Although these data indicate that atypical herpes-like viruses are cosmopolitan and common in stony corals, their absolute abundance is not constant. For example, in corals from the Hawaiian island of Oahu, various forms of chemical and physical stress increased the relative and absolute abundances of sequences similar to herpes-like viruses[110,113]. In fact, temperature and nutrient stress increased the absolute abundance of these viruses by several orders

Microbialization
The hypothesis that a habitat that experiences various stressors is altered through shifts in carbon to lower (microbial) trophic levels.

Horizontal gene transfer
The movement of genes between or among organisms in the absence of reproduction that occurs through several mechanisms, including phage infection.

Transduction
The transfer of genetic material between bacteria through phage infection.

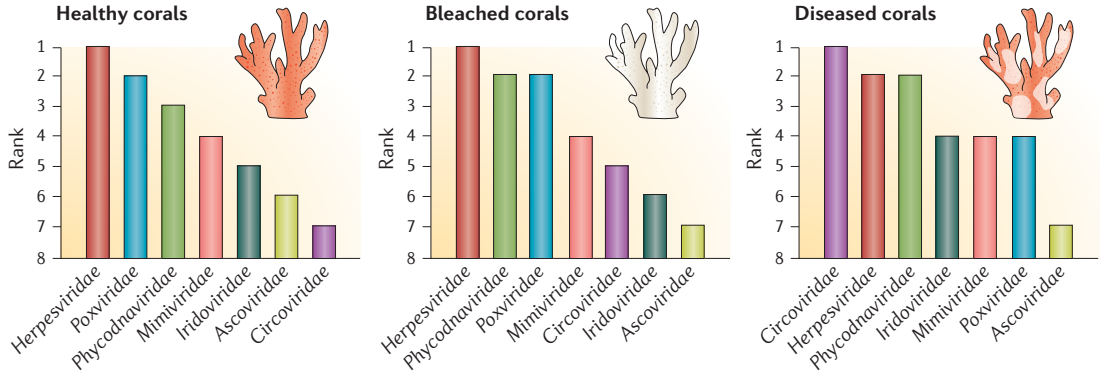

Figure 4 | **Changes in the relative abundance of members of the core coral virome with coral health state.** For each coral health state, the dominant virus families are ordered from highest to lowest number of sequence similarities recovered. Note that members of the *Circoviridae* are dominant in diseased stony corals, but not in healthy or bleached corals. Members of the *Phycodnaviridae*, the putative hosts of which are *Symbiodinium* spp. (dinoflagellate algal endosymbionts of corals), are more abundant in bleached corals than in healthy and diseased corals. Interestingly, a similar pattern is not observed in the *Mimiviridae* family, the members of which are also hypothesized to infect *Symbiodinium* spp. Data from REFS 46,53,56,57,110,162,163.

of magnitude compared with unstressed corals, which highlights the role of these herpes-like viruses in disease and mortality.

Shifts in the dominant virus families based on the relative abundances of sequences provide insights into the virus families that may have a role in coral disease and mortality. Such shifts were found for the *Phycodnaviridae* and *Circoviridae* families in stressed corals (FIG. 4). Members of the *Circoviridae* became the most abundant viruses in corals with signs of white plague, a common disease of corals that has no known aetiological agent. By contrast, members of the *Phycodnaviridae*, a family of NCLDVs that are known to infect microalgae, moved up one rank and became the second-most abundant viruses in bleached corals, which suggests that they have a role in the destruction of algal symbionts or the dysfunction of symbiont–host mutualism. Phycodnaviruses are prevalent in healthy and heat-stressed corals[53] and in *Symbiodinium* spp. isolates[45,53] (FIG. 1g,h). The similarity of these NCLDVs to taxa that infect phytoplankton and their presence in both heat-stressed corals and cultures of *Symbiodinium* spp. supports their role in bleaching, although the extent of such infections is unknown.

Shifts in total and relative abundances can indicate the importance of different groups of viruses, but responses by the host can also be signs of active infection. Recently, transcriptomic studies identified evidence of viral infection in heat-stressed and diseased corals[51,54,58,59,114]. Interestingly, the most-abundant transcripts during a white plague outbreak originated from phage and eukaryotic viruses[54]. Virus abundance can be four times higher in the water column just above diseased corals than in surface water[115], and during temperature stress, coral mucus-associated viral loads increased by approximately ten times[39]. Taken together, these experimental and observational studies indicate that virus outbreaks may be a common consequence of stress[46], particularly under high-temperature and/or nutrient-rich conditions.

Conclusions and outlook

Host and habitat: mechanism of enhanced virus-mediated declines of coral reefs. This Review highlights the connection between viral infection in reef hosts and concentrations of nutrients and community diversity in reef sea water[60]. Given that corals are ecosystem engineers, research that illuminates the roles of viruses in coral reef health or decline has important implications for the management and conservation of these ecosystems. Viruses modulate coral reef health both directly through disease and tissue loss and indirectly by altering energy fluxes and biogeochemical cycling. Thus, the release of cellular contents from corals and hosts in the water column can stimulate microbial blooms, and, in the process, can alter essential nutrient concentrations in the water column and benthos, which can stimulate subsequent viral production. Human actions that affect abiotic factors can initiate a feedback loop or vortex of reef decline that involves direct and indirect viral mechanisms (FIG. 5).

We suggest here that some environmental changes increase viral production in corals, which then leads to further degradation of reefs. Viral infections of both coral hosts and their microbiota can change the composition of viral consortia and lead to the transfer of nutrients from one reef compartment to another; thus, we argue that viral production in corals is likely to function as a 'revolving door' that connects the reef benthos to the adjacent water column. Specifically, anthropogenic drivers of viral production, such as eutrophication and thermal anomalies, increase viral production in corals to the detriment of the host and the habitat. Note that this may occur in the context of increased mucus production and release[22], increased microbial abundances on corals[29,60,116] and decreases in the ratio of autotrophic to heterotrophic bacteria on corals[29]. Autotrophic bacteria are likely to dampen the negative effects of heterotrophic bacteria on corals because autotrophs use more energy and nutrients[117]. Stress-induced viral infections can destroy coral tissues and *Symbiodinium* spp., which

Viral production
The release of new virus particles following host cell lysis due to viral infection.

Eutrophication
An increase of inorganic or organic nutrients (for example, nitrate, phosphate or sewage) in a habitat that results in negative ecosystem effects.

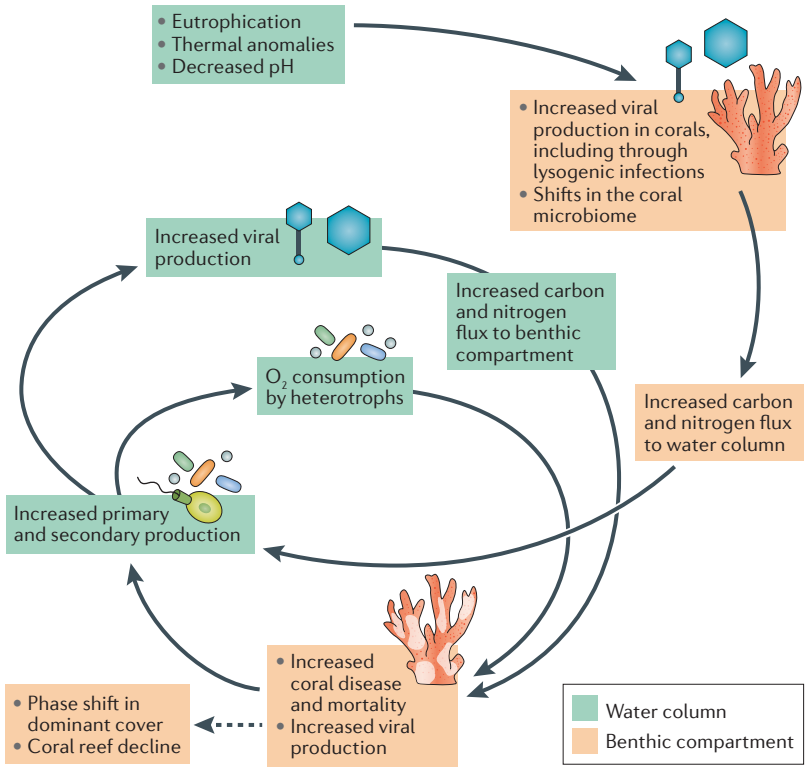

Figure 5 | **Overview of the virus-mediated vortex of coral reef decline.** We hypothesize that coral reef viruses can have a substantial effect on ecosystem function because nutrients that are released through viral lysis are readily transferred between the reef benthic and water column compartments (orange and green, respectively), as if through a 'revolving door'. When human actions generate stressful conditions on reefs (for example, thermal anomalies), this can trigger excessive microbial growth and viral production in coral colonies and result in the release of coral cellular contents (for example, mucus exudates) into the water column. At least some of these materials move from the benthic compartment to the water column, in which they can stimulate primary and ultimately secondary production. Increased abundances of heterotrophic bacteria can lead to oxygen drawdown in the water column adjacent to corals, which contributes to hypoxic conditions and colony mortality. Concurrently, viral lysis of autotrophic and heterotrophic microbial blooms in the water column results in additional carbon and nitrogen flux, which can be transferred to the benthic compartment of reefs and cause further shifts in microbial communities and viral production, and increased coral disease and mortality. The nutrients that are subsequently released then feed back on the ecosystem (for example, to increase primary and secondary production in the water column) and further degrade reefs. Stony coral die-off on reefs can ultimately result in a shift in dominant cover on reefs from scleractinian corals to macroalgae, sponges or soft corals (dashed arrow).

ultimately drives colony-derived carbon from the benthos into the water column in reef ecosystems. In the water column, these nutrients stimulate primary production, which may initially act as an energy sink and slow the increase in secondary (heterotrophic) production[117]. However, under chronic and/or high nutrient release, heterotrophic microbial growth in the water column is stimulated, which ultimately reduces levels of dissolved oxygen in the water column through respiration and contributes to further coral mortality (FIG. 5). Blooms of marine bacterioplankton also trigger viral production in reef waters, which leads to the release of further carbon and nitrogen. These elements can then pass through the revolving door from the water column to the benthos, in which they can trigger viral production, disease and mortality in corals, which enhances the feedback loops that precipitate coral reef decline (FIG. 5). Recent work also suggests that in reef ecosystems that have dense bacterial communities, lysogenic viruses are prevalent[70]. Piggyback-the-winner dynamics may provide coral-associated bacteria with virulence factors[70], which changes the nature of coral–bacterial symbiont interactions. The triggering of lysogenic conversion and viral production is also likely to increase remineralization rates and further contribute to this feedback loop.

We hypothesize that, at some point, as reefs continue along this virus-mediated vortex of decline, few healthy corals will remain to draw down carbon, nitrogen and other nutrients from the water column[117]. A shift may occur in which macroalgae, sponges or soft corals replace stony corals as the dominant benthic cover, which affects the fluxes of carbon and nitrogen from the benthos to the water column. Eventually, most energy may be pumped into the microbial loop, leading to complete microbialization of the habitat[118]. However, with restoration efforts and improvements of water quality, as well as reductions in the amount of CO_2 added to the atmosphere and other conservation efforts to preserve the health of reefs, coral reef ecosystems have the potential to avoid collapse.

***Better tools for the field, the lab and* in silico.** Despite many gains in our understanding of the role that viruses have in reef ecology, much remains unknown. Many of our challenges in understanding tropical reef virology involve methodology and reference data. As the field is still young, it lacks many of the molecular, genomic and manipulative tools to conduct both broad surveys and reductionist experiments. For example, in a similar way to many underexplored systems, we continue to generate sequence libraries with high percentages of reads (>50–70%) that do not have clear annotations — particularly for viromes from coral animals, for which almost no viral genome databases are available. Thus, phylogenetic analyses of viruses in corals remain constrained. Furthermore, measuring viral production in coral tissues is currently limited by working in a host-based system, whereas the standard techniques were developed in liquid and dark-adapted environments, although there has been some progress[111]. Viral production experiments, combined with pulse–chase experiments to track carbon and nitrogen flux, could provide strong evidence for the direct and indirect roles of viruses in the modulation of ecosystem-level processes.

The field of coral reef research must continue to develop better tools to study the activity, diversity and ecological effects of viruses in hosts and habitats. The field must also develop models of how environmental conditions change the interactions between viruses and their hosts. Last, the scientific community must develop reductionist models to test the hypotheses that are generated in survey-based studies. For example, the development of coral cell lines and algal cultures to propagate and manipulate coral and *Symbiodinium* spp. eukaryotic viruses is a priority. Such tools would enable us to characterize viral genomes and physiology comprehensively

and accurately. At the same time, these tools would enable tests of how viruses affect symbiotic state and the cell cycle in their hosts.

As discussed above, estimates of virus–host dynamics in coral reef systems lead us to hypothesize that a 'viral vortex' may affect overall reef health. Given the large abundances of viruses and their potential effects on corals, *Symbiodinium* spp. and bacterial hosts, we suggest that viruses contribute to reef decline through two mechanisms: direct host mortality through infection and subsequent cell or tissue lysis; and indirect host mortality through viral-mediated alterations in the flux of dissolved and particulate matter in the environment. This flux drives oligotrophic reef ecosystems to be more productive, ultimately resulting in undesirable community shifts and the loss of reef integrity, resilience and function.

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Competing interests statement
The authors declare no competing interests.